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To:

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in its capacity as elected Office

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Applicant: HAYAKAWA, Eiji et al	

1. The designated Office is hereby notified of its election made:

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07 April 1999 (07.04.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

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特　許　協　力　条　約

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国際予備審査報告の送付の通知書

（法施行規則第５７条）
〔ＰＣＴ規則71.1〕

発送日（日.月.年）	07.03.00

出願人又は代理人の書類記号	１１１３２	重要な通知

国際出願番号	国際出願日（日.月.年）	優先日（日.月.年）
ＰＣＴ／ＪＰ９９／０１８６１	０７．０４．９９	０８．０４．９８

出願人（氏名又は名称）
協和醗酵工業株式会社

１．国際予備審査機関は、この国際出願に関して国際予備審査報告及び付属書類が作成されている場合には、それらをこの送付書とともに送付することを、出願人に通知する。

２．国際予備審査報告及び付属書類が作成されている場合には、すべての選択官庁に通知するために、それらの写しを国際事務局に送付する。

３．選択官庁から要求があったときは、国際事務局は国際予備審査報告（付属書類を除く）の英語の翻訳文を作成し、それをその選択官庁に送付する。

４．注　意

出願人は、各選択官庁に対し優先日から３０月以内に（官庁によってはもっと遅く）所定の手続（翻訳文の提出及び国内手数料の支払い）をしなければならない（ＰＣＴ３９条（１））（様式ＰＣＴ／ＩＢ／３０１とともに国際事務局から送付された注を参照）。

国際出願の翻訳文が選択官庁に提出された場合には、その翻訳文は、国際予備審査報告の付属書類の翻訳文を含まなければならない。
この翻訳文を作成し、関係する選択官庁に直接送付するのは出願人の責任である。

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名称及びあて名	権限のある職員	３Ｅ	８８２５
日本国特許庁（ＩＰＥＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	特　許　庁　長　官 電話番号　０３－３５８１－１１０１　内線　３３４５		

様式ＰＣＴ／ＩＰＥＡ／４１６（１９９２年７月）　　（添付用紙の注意書きを参照）

注　　意

1．文献の写しの請求について
国際予備審査報告に記載された文献であって国際調査報告に記載されていない文献の複写
特許庁にこれらの引用文献の写しを請求することができますが、日本特許情報機構でもこれらの引用文献の複写物を販売しています。日本特許情報機構に引用文献の複写物を請求する場合は下記の点に注意してください。
〔申込方法〕
（１）特許（実用新案・意匠）公報については、下記の点を明記してください。
○特許・実用新案及び意匠の種類
○出願公告又は出願公開の年次及び番号（又は特許番号、登録番号）
○必要部数
（２）公報以外の文献の場合は、下記の点に注意してください。
○国際予備審査報告の写しを添付してください（返却します）。
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〒１００　東京都千代田区霞が関３－４－２　商工会館・弁理士会館ビル
財団法人　日本特許情報機構　サービス課
ＴＥＬ　０３－３５０３－３９００
注）　特許庁に対して文献の写しの請求をすることができる期間は、国際出願日から７年です。

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特　許　協　力　条　約

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EP　US　国際調査報告

（法8条、法施行規則第40、41条）
〔ＰＣＴ１８条、ＰＣＴ規則43、44〕

出願人又は代理人 の書類記号　１１１３２	今後の手続きについては、国際調査報告の送付通知様式（ＰＣＴ／ＩＳＡ／２２０）及び下記５を参照すること。	
国際出願番号 ＰＣＴ／ＪＰ９９／０１８６１	国際出願日 （日.月.年）　０７．０４．９９	優先日 （日.月.年）　０８．０４．９８
出願人（氏名又は名称） 協和醗酵工業株式会社		

国際調査機関が作成したこの国際調査報告を法施行規則第41条（ＰＣＴ１８条）の規定に従い出願人に送付する。
この写しは国際事務局にも送付される。

この国際調査報告は、全部で　2　ページである。

☐ この調査報告に引用された先行技術文献の写しも添付されている。

１．国際調査報告の基礎

ａ．言語は、下記に示す場合を除くほか、この国際出願がされたものに基づき国際調査を行った。
☐ この国際調査機関に提出された国際出願の翻訳文に基づき国際調査を行った。

ｂ．この国際出願は、ヌクレオチド又はアミノ酸配列を含んでおり、次の配列表に基づき国際調査を行った。
☐ この国際出願に含まれる書面による配列表
☐ この国際出願と共に提出されたフレキシブルディスクによる配列表
☐ 出願後に、この国際調査機関に提出された書面による配列表
☐ 出願後に、この国際調査機関に提出されたフレキシブルディスクによる配列表
☐ 出願後に提出した書面による配列表が出願時における国際出願の開示の範囲を超える事項を含まない旨の陳述書の提出があった。
☐ 書面による配列表に記載した配列とフレキシブルディスクによる配列表に記録した配列が同一である旨の陳述書の提出があった。

２．☐ 請求の範囲の一部の調査ができない（第Ⅰ欄参照）。

３．☐ 発明の単一性が欠如している（第Ⅱ欄参照）。

４．発明の名称は
☒ 出願人が提出したものを承認する。
☐ 次に示すように国際調査機関が作成した。

５．要約は
☒ 出願人が提出したものを承認する。
☐ 第Ⅲ欄に示されているように、法施行規則第47条（ＰＣＴ規則38.2(b)）の規定により国際調査機関が作成した。出願人は、この国際調査報告の発送の日から１カ月以内にこの国際調査機関に意見を提出することができる。

６．要約書とともに公表される図は、
第　2　図とする。☐ 出願人が示したとおりである。　☐ なし
☐ 出願人は図を示さなかった。
☒ 本図は発明の特徴を一層よく表している。

国際調査報告

国際出願番号 PCT／JP99／01861

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cl⁶ A61J 3／10

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl⁶ A61J 3/10, B30B 11/00 11/08, A61K 9/00-9/72 47/00-47/48

最小限資料以外の資料で調査を行った分野に含まれるもの

日本国実用新案公報 1922－1996年
日本国公開実用新案公報 1971－1999年
日本国登録実用新案公報 1994－1999年
日本国実用新案登録公報 1996－1999年

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

C. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
Y	JP, 45-22959, B1 (カーター・ワレス・インコーポレーテッド) 3.8月.1970(03.08.70) 第1欄第26行－第2欄第6行 (ファミリーなし)	1, 3, 5-10 12-14
Y	JP, 7-124231, A (協和醗酵工業株式会社) 16.5月.1995(16.05.95) 全文, 全図 &EP, 650826, A1&US, 5700492, A	1－14
Y	JP, 2-206, A (藤沢薬品工業株式会社) 5.1月.1990(05.01.90) 全文 &EP, 315964, A&US, 5093372, A	2, 4-9, 11-14
Y	JP, 62-187598, A (ユニバーシティ オブ バス) 15.8月.1987(15.08.87) 全文, 全図 &GB, 2183538, A&EP, 225803, A&US, 4832880, A	1－14
Y	JP, 8-277218, A (協和醗酵工業株式会社) 22.10月.1996(22.10.96) 請求項1, 3, 図1, 2 (ファミリーなし)	6, 13, 14

☐ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

＊ 引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日 08.07.99	国際調査報告の発送日 21.07.99
国際調査機関の名称及びあて先 日本国特許庁（ISA／JP） 郵便番号100－8915 東京都千代田区霞が関三丁目4番3号	特許庁審査官（権限のある職員） 大橋 賢一 3E 8825 電話番号 03－3581－1101 内線 3345

様式PCT／ISA／210（第2ページ）（1998年7月）

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世界知的所有権機関
国際事務局

特許協力条約に基づいて公開された国際出願

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(30) 優先権データ
特願平10/96441 1998年4月8日(08.04.98) JP

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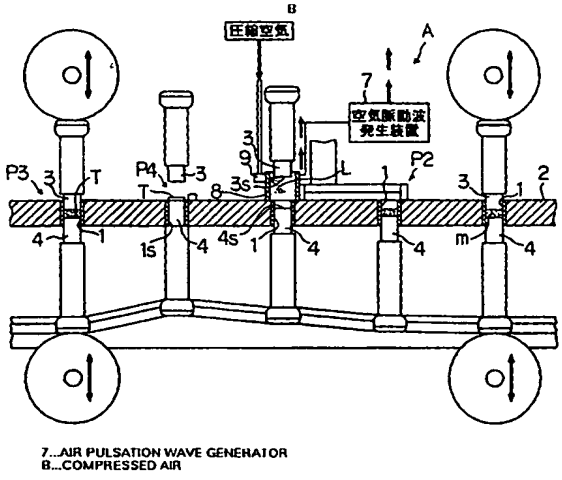
(81) 指定国 AU, BG, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, VN, ZA, 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)

添付公開書類
国際調査報告書

(54)Title: TABLET MANUFACTURING METHOD AND TABLET

(54)発明の名称 錠剤の製造方法及び錠剤



7...AIR PULSATION WAVE GENERATOR
8...COMPRESSED AIR

(57) Abstract

A tablet manufacturing method for manufacturing tablets by compression-molding molding materials using a mortar and a mallow, comprising the steps of using powder and granular materials containing powder and granular compounds degenerated or deactivated when compressed under high pressure, housing the mortar and the mallow in a spray room, generating air pulsation wave and spraying an air-mixed lubricant within the spray room, applying the lubricant to the surfaces of the mortar and the mallow with the sprayed lubricant mixed with the generated air pulsation wave, and compressing the molding materials using the lubricant-coated mortar and the lubricant-coated mallow.

(57)要約

本発明に係る錠剤の製造方法は、成形材料を、杵と臼とを用いて圧縮成形して錠剤を製造する、錠剤の製造方法であって、前記成形材料として、高圧で打錠すると変性又は失活する化合物の粉粒体を含む粉粒体材料を用い、前記杵と前記臼とを散布室内に収容し、前記散布室内に、空気脈動波を発生させるとともに、空気に混和した滑沢剤を噴霧し、前記散布室内に噴霧された滑沢剤を、前記空気脈動波に混和し、前記空気脈動波に混和した状態下で、前記杵の表面及び前記臼の表面に、前記滑沢剤を塗布し、前記滑沢剤が表面に塗布された杵と、前記滑沢剤が表面に塗布された臼とを用いて、前記成形材料を打錠するようにしている。

明　細　書

錠剤の製造方法及び錠剤

技術分野

本発明は、錠剤の製造方法に関し、特に、高圧で打錠すると変性又は失活する化合物粉粒体を含有する錠剤を、薬物を変性又は失活させることなく製造することができる錠剤の製造方法、並びに、固体分散体粉粒体を含有する錠剤を、錠剤中に含まれる固体分散体の機能を保持したまま錠剤を製造することができる錠剤の製造方法に関する。

また、本発明は、錠剤に関し、高圧で打錠すると変性又は失活する化合物粉粒体を変性又は失活させることなく含有している錠剤、並びに、固体分散体粉粒体を、その機能を保持したまま含有している錠剤に関する。

背景技術

錠剤は、服用が簡単であるといった利点があり、内服用、口腔用等として患者に最も好まれる剤形である。

このような錠剤は、一般に内部滑沢法や外部滑沢法によって製造されている。

ここに、内部滑沢法は、打錠機の杵と臼とを用いて成形材料を打錠して錠剤を製造する工程において、杵や臼に、打錠する成形材料が付着したり、杵臼間にギシツキが生じたりするのを防止して、円滑な打錠が行えるようにするためや、錠剤に、スティッキングやキャッピングやラミネーションを生じた不良品が発生するのを防止する目的として、打錠する成形材料中に、有効成分や賦形剤の他に、ステアリン酸マグネシウム、ラウリル硫酸ナトリウム、タルク等の滑沢剤を混練し、これを圧縮成形して錠剤を製造する錠剤の製造方法をいう。

また、外部滑沢法としては、例えば、特公昭４１－１１２７３号公報や、特開昭５６－１４０９８号公報に記載の錠剤の製造方法が、既に、提案されている。

図１７は、特公昭４１－１１２７３号公報に記載の錠剤の製造方法を概略的に示す工程図である。

この錠剤の製造方法は、錠剤化すべき材料の所定量を臼内に充填する工程と、

臼内に充填された材料を上下１組の杵を用いて圧縮して、錠剤化する工程と、錠剤を排出する工程とを備える、錠剤の製造方法において、図１７（ａ）に示すように、臼１５１内に成形材料を充填する工程の前段の工程として、臼１５１の上方所定位置に、滑沢剤Ｌを噴射する噴射ノズル１５９を設置し、噴射ノズル１５９が設置されている位置にきた臼１５１に対応して設けられた上杵１５３の下端面１５３ｓ及び下杵１５４の上端面１５４ｓに対して、噴射用ノズル１５９から滑沢剤Ｌを噴射させて、滑沢剤Ｌを塗布し、その後、図１７（ｂ）に示すように、臼１５１内に成形材料を充填し、臼１５１内に充填された成形材料ｍを、図１７（ｃ）に示すように、下端面１５３ｓに滑沢剤Ｌが塗布された上杵１５３と、上端面１５４ｓに滑沢剤Ｌが塗布された下杵１５４とを用いて圧縮し、錠剤を製造するようにしている。

尚、図１７中、１５２で示す部材は、臼１５１を設けた、回転テーブルを示している（以下、図１８において同じ）。

また、図１８は、特開昭５６－１４０９８号公報に記載される、錠剤の製造方法を概略的に示す工程図である。

この錠剤の製造方法は、臼１５１内に成形材料を充填する工程の前段工程において、臼１５１の上方所定位置に、滑沢剤Ｌを散布する散布器１５６、及び、エアを噴射するノズル１５９を設け、図１８（ａ）に示すように、散布器１５６が設置された位置にきた臼１５１に、散布器１５６内に滑沢剤Ｌを散布することで、図１８（ｂ）に示すように、この臼１５１に対応して設けられた下杵１５４の上端面１５４ｓに滑沢剤Ｌを載置した後、図１８（ｃ）に示すように、ノズル１５９が設けられた位置で、ノズル１５９から下杵１５４に対して圧縮エアを噴射して、下杵１５４の上端面１５４ｓ上に載置されている滑沢剤Ｌを上方へ吹き飛ばして離散させ、この離散した滑沢剤Ｌを臼１５１の内周面１５１ｓや上杵１５３の下端面１５３ｓに付着させ、その後、臼１５１の内周面１５１ｓ、上杵１５３の下端面１５３ｓ及び下杵１５４の上端面１５４ｓに滑沢剤Ｌが塗布臼１５１、上杵１５３及び下杵１５４を用いて、成形材料ｍを圧縮して錠剤を製造するようにしている。

しかしながら、薬物の中には、打錠の際に加えられる圧力（通常、１トン（ｔ

ｏｎ）／ｃｍ^2～２トン（ｔｏｎ）／ｃｍ^2）や、摩擦や、熱等により結晶に歪みを生じ、不安定化したり、分解したり、また、溶出が遅くなるものがある（以下、このような薬物を、本明細書では、「高圧で打錠すると変性又は失活する薬物」という）。

このような薬物を錠剤化する方法としては、マクロゴール６０００、ショ糖脂肪酸エステル等の滑沢剤を成形材料中に添加する内部滑沢法が既に提案されている（牧野 正他、第１１回製剤と粒子設計シンポジウム講演要旨集、７９（１９９４）、特開平８－１７５９９６号公報を参照）。

また、近年、薬物を低分子あるいは高分子担体中に単分子分散させた固体分散体製剤も開発されている。

固体分散体製剤は、特に、難溶性で、経口投与した場合、体内への吸収性の低い薬物の溶解度を高めたり、薬物の放出速度をコントロールしたり、バイオアベイラビリティーを向上させたりするのに非常に有効である。

固体分散体製剤は、一般に、薬物と担体を加熱溶融し、その後、冷却して製造する溶融法や、薬物と担体とを適当な溶媒に溶解した後、溶媒を除去する溶媒法や、溶融法と溶媒法とを組み合わせた、溶融－溶媒法等によって製造されている。

しかしながら、高圧で打錠すると変性又は失活する薬物を含有する錠剤を、マクロゴール６０００及びショ糖脂肪酸エステル等の滑沢剤を成形材料中に添加して製造する内部滑沢法は、汎用できる方法ではなく、薬物によっては、マクロゴール６０００、ショ糖脂肪酸エステル等の滑沢剤を成形材料中に添加しても、打錠後の薬物が不安定化したり、分解したり、また、溶出が遅くなるものがある。

更には、薬物によっては、打錠時に、杵や臼に付着し易く、この結果、製造される錠剤に、スティッキングやキャッピングやラミネーションを起こしてしまうものがある。

また、固体分散体製剤として、固体分散体を適当な粒径に粉砕した後、固体分散体粉粒体と滑沢剤とを混練し、従来の内部滑沢法により、固体分散体の錠剤を製造すると、錠剤内部に含まれる滑沢剤の撥水性等により、固体分散体の錠剤の物性が変化したり、錠剤内部に滑沢剤を含ませると、錠剤に実用的な硬度をだすようにするためには、高い打錠圧を用いなければならず、固体分散体自体が、こ

の高い打錠圧によって変性してしまい、当初の設計通りの物性（例えば、崩壊時間等）を示さなくなるという問題がある。

このため、従来は、高圧で打錠すると変性又は失活する薬物を含む製剤や、固体分散体の製剤は、一般に、カプセル剤として、市場に供給されている。

しかしながら、カプセル剤は、服用時に、水と一緒に服用すると、水に浮くため、特に、老人や小児にとって、服用しづらく、臨床家等から、高圧で打錠すると変性又は失活する薬物や、固体分散体の製剤として、水と一緒に服用すると、水に沈んで、嚥下しやすい、錠剤を開発して欲しい、との要望がある。

また、カプセル剤は、カプセルのボディとキャップを必要とし、また、製造する際に、一々、カプセルのボディに、適当な粒径に粉砕した、高圧で打錠すると変性又は失活する薬物や固体分散体粉粒体（粉末、顆粒）を充填し、その後、キャップをかぶせて封緘して製造する必要があるため、製造に手間がかかるという問題がある。

更に、臨床家等からは、従来、カプセル剤として、市場に供給されているものを、単に、錠剤にするだけでなく、そのような錠剤が、患者等に応じて最適な服用量にできるように、分割可能な錠剤にして欲しい、という要望もある。

本発明は、以上のような問題を解決するためになされたものであって、高圧で打錠すると変性又は失活する化合物粉粒体を含有する錠剤を、錠剤中に含まれる、そのような薬物を変性又は失活させることなく容易に製造することができる錠剤の製造方法を提供することを目的とする。

また、錠剤中に含まれる固体分散体の機能が保持された、固体分散体粉粒体を含有する錠剤、高圧で打錠すると変性又は失活する化合物を変性又は失活させることなく含有する錠剤、及び、そのような錠剤であって、分割しても機能が保持された分割可能な錠剤を提供することを目的とする。

発明の開示

請求項１に記載の錠剤の製造方法は、成形材料を、杵と臼とを用いて圧縮成形して錠剤を製造する、錠剤の製造方法であって、成形材料として、高圧で打錠すると変性又は失活する化合物の粉粒体を含む粉粒体材料を用い、杵と臼とを散布室内に収容し、散布室内に、空気脈動波を発生させるとともに、空気に混和した

滑沢剤を噴霧し、散布室内に噴霧された滑沢剤を、空気脈動波に混和し、空気脈動波に混和した状態下で、杵の表面及び前記臼の表面に、滑沢剤を塗布し、滑沢剤が表面に塗布された杵と、滑沢剤が表面に塗布された臼とを用いて、成形材料を打錠するようにした。

ここに、本明細書で用いる「高圧」は、内部滑沢法を用いて成形材料を圧縮し、実用的な硬度の錠剤を製造するのに必要な打錠圧を意味し、より具体的には、1トン（ｔｏｎ）／ｃｍ^{2}以上を意味する。

また、「高圧で打錠すると変性又は失活する化合物の粉粒体」は、内部滑沢法を用いて、化合物粉粒体を打錠すると、化合物が変性したり、失活したりする化合物の粉粒体を意味する。具体的に、そのような化合物を例示すると、後述する、表３～表６に示すような薬物を挙げることができる。

また、「高圧で打錠すると変性又は失活する化合物の粉粒体を含む粉粒体材料」は、高圧で打錠すると変性又は失活する化合物の粉粒体の他に、賦形剤や、必要により、結合剤、溶解補助剤や可溶化剤や崩壊剤等の補助剤、矯味剤、着色剤、製剤用添加剤、抗酸化剤、保存剤、遮光剤、帯電防止剤、芳香剤、甘味剤、流動化剤、香味剤等を含んでいても良いが、滑沢剤は含まない粉粒体材料を意味する。

この錠剤の製造方法では、杵及び臼に、空気脈動波を発生させた散布室内に滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を空気脈動波に混和させて、塗布するようにしたので、従来の外部滑沢法に比べ、杵の表面及び臼の表面に、滑沢剤を均一に塗布できる。

この結果、高圧で打錠すると変性又は失活する化合物粉粒体を打錠する工程において、杵の表面及び臼の表面に、高圧で打錠すると変性又は失活する化合物粉粒体が付着し難くなり、製造される生物学的製剤の錠剤に、スティッキングや、キャッピングや、ラミネーティング等を生じ難い。

且つ、錠剤の表面に滑沢剤が付着しているに過ぎず、その内部には、滑沢剤が含まれていないため、滑沢剤を内部に含む錠剤に比べ、低い打錠圧（具体的には、１トン（ｔｏｎ）／ｃｍ^{2}未満の打錠圧）を用いて、高圧で打錠すると変性又は失活する化合物粉粒体を打錠しても、製造される錠剤は、実用レベルの硬度を有する。

尚、本発明に係る錠剤の製造方法で用いる滑沢剤としては、種々のものを用いることができ、特に限定されることはないが、例えば、ステアリン酸金属塩（ステアリン酸マグネシウム、ステアリン酸カルシウム等）、ステアリン酸、ラウリル硫酸ナトリウム、ラウリル硫酸マグネシウム、アラビアゴム末、カルナウバロウ、無水珪酸、酸化マグネシウム、珪酸水和物、デンプン、ホウ酸、脂肪酸ナトリウム塩、ロイシン等の通常用いられる滑沢剤であれば、いずれをも使用することができ、目的に応じて、単独で使用しても、これらの滑沢剤を２以上組み合わせて使用してもよい。

また、賦形剤は、種々のものを用いることができ、糖類（乳糖、白糖、ブドウ糖、マンニトール等）、デンプン（例えば、バレイショ、コムギ、トウモロコシ等）、無機物（炭酸カルシウム、硫酸カルシウム、炭酸水素ナトリウム、塩化ナトリウム等）、結晶セルロース、植物末（カンゾウ末、ゲンチアナ末等）を挙げることができる。

また、空気脈動波としては、その空気圧が、正圧、負圧のいずれを問わず、散布室内の全域に空気振動を生じさせて、散布室内に噴霧された滑沢剤の粒子を強制的に拡散させる作用を発揮するものであれば、種々の周期、種々の強度の空気脈動波を用いることができる。

このような空気脈動波の周波数や圧力等の条件は、打錠機の杵や臼の大きさや形状、散布室の大きさや形状、滑沢剤の噴霧手段、滑沢剤の噴霧手段の設けられ方、有効成分の性状等によっても異なってくるので一概には規定できず、実験に基づいて規定される。

請求項２に記載の錠剤の製造方法は、成形材料を、杵と臼とを用いて圧縮成形して錠剤を製造する、錠剤の製造方法であって、成形材料として、固体分散体粉粒体を用い、杵と臼とを散布室内に収容し、散布室内に、空気脈動波を発生させるとともに、空気に混和した滑沢剤を噴霧し、散布室内に噴霧された滑沢剤を、空気脈動波に混和し、空気脈動波に混和した状態下で、杵の表面及び臼の表面に、滑沢剤を塗布し、滑沢剤が表面に塗布された杵と、滑沢剤が表面に塗布された臼とを用いて、成形材料を打錠するようにした。

ここに、本明細書で用いる「固体分散体粉粒体」は、固体分散体を適当な粒径

に粉砕した固体分散体（粉末または顆粒）を意味する。

より具体的に説明すると、この錠剤の製造方法は、例えば、内部滑沢法による打錠時の高い圧力では溶出が遅延する低分子薬物、分解や変性を受け易い高分子薬物を含む固体分散体粉粒体を錠剤にするのに効果的である。

固体分散体の担体としては、いわゆる高分子担体を用いることができる。

高分子担体としては、一般に、ｐＨ依存性高分子担体、ｐＨ非依存性高分子担体、水溶性高分子担体等があり、例えば、以下のような高分子化合物を上げることができる。

即ち、ヒドロキシプロピルメチルセルロースフタレート２２０８２４（ＨＰ５０）、ヒドロキシプロピルメチルセルロースフタレート２２０７３１（ＨＰ５５）、ヒドロキシプロピルメチルセルロースアセテートサクシネート（Ａコート）、カルボキシメチルエチルセルロース（ＣＭＢＣ）、酢酸フタル酸セルロース（ＣＡＰ）、メタアクリル酸コポリマーＬＤ（Ｌ３０Ｄ５５）、メタアクリル酸コポリマーＳ（Ｓ－１００）、アミノアルキルメタアクリレートコポリマーＥ（胃溶性）、ポリビニルアセタールジエチルアミノアセテート（ＡＢＡ）、ポリビニルピロリドン（Ｋ－２５、３０、９０；ＰＶＰ）、エチルセルロース（ＢＣ）、メタアクリル酸コポリマーＲＳ（ＲＳ３０Ｄ）、ポリビニルアルコール（ＰＶＡ）、メチルセルロース（ＭＣ）、ヒドロキシプロピルセルロース（ＨＰＣ）、ヒドロキシプロピルメチルセルロース２２０８（メトローズ９０ＳＨ）、ヒドロキシプロピルメチルセルロース２９０６（メトローズ６５ＳＨ）、ヒドロキシプロピルメチルセルロース２９１０（メトローズ６０ＳＨ、ＴＣ－５Ｒ）、カルボキシメチルセルロースナトリウム（繊維素グリコール酸ナトリウム）、デキストリン、プルラン、アラビアゴム、トラガント、アルギン酸ナトリウム、アルギン酸プロピレングリコールエステル、カンテン末、ゼラチン、澱粉類、加工澱粉、リン脂質（レシチン）、グルコマンナン等を挙げることができる。

これらの高分子担体は、そのいずれかを単独で使用しても良く、必要により２種以上を混合して使用してもよい。

高分子担体の粒子径の大きさは、通常、７０００μｍ以下が適当であるが、好ましくは、２０００μｍ以下である。本発明の製造方法における圧力、温度、供

給速度、水又は可塑剤の添加量及び供給速度等の設定条件は、使用する薬物、高分子担体、２軸型エクストルーダーの種類やその他の条件等によって異なるが、薬物や高分子担体の分解温度以下になるように各々を組み合わせることが重要で、目的とする製品特性に応じて変化させることが必要である。

薬物と高分子担体を混合するときの比率（重量比率）は、薬物や高分子担体の種類、目的、膜特性等によって異なるが、薬物１に対して、高分子担体が０．１から９９９、好ましくは０．５から５００、更に好ましくは１から５０が適当である。

熱に不安定な薬物又は高分子担体を含んだ系においては、可塑剤の水溶液又は分散液を２軸型エクストルーダーにかける前又はかけている途中に添加することができる。この方法を利用すれば高分子担体の転移温度を低下させることができるので、成形温度を薬物及び高分子担体分解温度以下に設定することができ、薬物や高分子担体等の熱による分解を防ぐことができる。もちろん熱に不安定な薬物又は高分子担体を含んでいない系においても、可塑剤の水溶液又は分散液を同じように添加することができることはいうまでもない。

この高分子担体の転移温度を低下させるための可塑剤としては、製剤分野においてフィルムコーティング剤の可塑剤として利用されている化合物等を使用することができる。例えば、以下のような化合物を挙げることができる。

即ち、可塑剤として、セタノール、中鎖脂肪酸トリグリセライド、ポリオキシエチレンーポリオキシプ、マクロゴール類（２００、３００、４００、６００、１０００、１５００、１５４０、４０００、６０００、２００００）、トリアセチン、クエン酸トリエチル（シトロフレックス）等をその具体例として挙げることができる。

可塑剤の添加量としては、使用する薬物や高分子担体等によって異なるが、高分子担体に対し１％から８０％が適当であり、好ましくは、５％から５０％が適当である。

また、その添加方法は、最初から高分子担体と薬物の混合物系に直接加えてもよいし、成形中に水に溶解又は分散させたものを添加してもよい。このように可塑材の添加方法は、特に限定されるものではない。

この錠剤の製造方法では、杵及び臼に、空気脈動波を発生させた散布室内に滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を空気脈動波に混和させて、塗布するようにしたので、従来の外部滑沢法に比べ、杵の表面及び臼の表面に、滑沢剤を均一に塗布できる。

この結果、固体分散体粉粒体を打錠する工程において、杵の表面及び臼の表面に、成形材料が付着し難くなり、製造される固体分散体の錠剤に、スティッキングや、キャッピングや、ラミネーティング等を生じ難い。

しかも、製造される固体分散体の錠剤は、その表面に滑沢剤が付着しているに過ぎず、その内部には、滑沢剤が含まれていないため、滑沢剤を内部に含む固体分散体の錠剤に比べ、低い打錠圧を用いて、固体分散体粉粒体を打錠しても、製造される固体分散体の錠剤は、実用レベルの硬度を有する。

したがって、この錠剤の製造方法を用いれば、低い打錠圧で、固体分散体の錠剤を製造できるので、固体分散体の物性が変化することがない。

請求項３に記載の錠剤の製造方法は、杵と臼とを用いて圧縮成形して錠剤を製造する、錠剤の製造方法であって、成形材料として、高圧で打錠すると変性又は失活する化合物の粉粒体を含む粉粒体材料を用い、杵と臼とを散布室内に収容し、散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を塗布し、滑沢剤が表面に塗布された杵と、滑沢剤が表面に塗布された臼とを用いて、成形材料を打錠するようにした。

この錠剤の製造方法では、散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を塗布するようにしたので、従来の外部滑沢法に比べ、杵の表面及び臼の表面に、滑沢剤を均一に塗布できる。

この結果、高圧で打錠すると変性又は失活する化合物粉粒体を打錠する工程において、杵の表面及び臼の表面に、高圧で打錠すると変性又は失活する化合物粉粒体が付着し難くなり、製造される生物学的製剤の錠剤に、スティッキングや、キャッピングや、ラミネーティング等を生じ難い。

且つ、錠剤の表面に滑沢剤が付着しているに過ぎず、その内部には、滑沢剤が含まれていないため、滑沢剤を内部に含む錠剤に比べ、低い打錠圧（具体的には、１トン（ｔｏｎ）／ｃｍ^{2}未満の打錠圧）を用いて、高圧で打錠すると変性又は失

活する化合物粉粒体を打錠しても、製造される錠剤は、実用レベルの硬度を有する。

請求項４に記載の錠剤の製造方法は、成形材料を、杵と臼とを用いて圧縮成形して錠剤を製造する、錠剤の製造方法であって、成形材料として、固体分散体粉粒体を用い、杵と臼とを散布室内に収容し、散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を塗布し、滑沢剤が表面に塗布された杵と、滑沢剤が表面に塗布された臼とを用いて、成形材料を打錠するようにした。

この錠剤の製造方法では、散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を塗布するようにしたので、従来の外部滑沢法に比べ、杵の表面及び臼の表面に、滑沢剤を均一に塗布できる。

この結果、固体分散体粉粒体を打錠する工程において、杵の表面及び臼の表面に、成形材料が付着し難くなり、製造される固体分散体の錠剤に、スティッキングや、キャッピングや、ラミネーティング等を生じ難い。

しかも、製造される固体分散体の錠剤は、その表面に滑沢剤が付着しているに過ぎず、その内部には、滑沢剤が含まれていないため、滑沢剤を内部に含む固体分散体の錠剤に比べ、低い打錠圧を用いて、固体分散体粉粒体を打錠しても、製造される固体分散体の錠剤は、実用レベルの硬度を有する。

したがって、この錠剤の製造方法を用いれば、低い打錠圧で、固体分散体の錠剤を製造できるので、固体分散体の物性が変化することがない。

請求項５に記載の錠剤の製造方法は、請求項１～４のいずれかに記載の錠剤の製造方法の、散布室内に噴霧する滑沢剤の噴霧量を、一錠剤当り、０．０００１重量％以上０．２重量％以下になるようにした。

錠剤の崩壊時間が延長したり、硬度が低下したりするのを防止するためには、滑沢剤の使用量は少なければ少ない方が好ましく、打錠する錠剤の一錠当りの使用量を、０．０００１重量％以上０．２重量％以下とするのが好ましく、０．００１重量％以上０．１重量％以下とするのが更に好ましい。

この錠剤の製造方法では、打錠する錠剤の一錠当りの使用量を、０．０００１重量％以上０．２重量％以下となるようにしたので、錠剤の崩壊時間が延長した

り、硬度が低下したりしない。

請求項６に記載の錠剤の製造方法は、請求項１～５のいずれかに記載の錠剤の製造方法に用いる、杵には、錠剤に割線を形成する突条が設けられている。

この錠剤の製造方法では、錠剤に割線を形成する突条を設けた杵を用いているので、高圧で打錠すると変性又は失活する化合物の粉粒体を含む分割可能錠剤や、機能が損なわれていない固体分散体粉粒体を含む分割可能錠剤を容易に製造することができる。

請求項７に記載の錠剤の製造方法は、請求項１又は請求項２に記載の錠剤の製造方法の、杵と臼とを散布室内に収容する工程、散布室内に、空気脈動波を発生させるとともに、空気に混和した滑沢剤を噴霧し、散布室内に噴霧された滑沢剤を、空気脈動波に混和し、空気脈動波に混和した状態下で、杵の表面及び臼の表面に、滑沢剤を塗布する工程、及び、滑沢剤が表面に塗布された杵と、滑沢剤が表面に塗布された臼とを用いて、成形材料を打錠する工程を、連続して行うことを特徴とする。

この錠剤の製造方法では、打錠工程において、スティッキング等が生じないことを利用して、連続打錠するようにしているので、高圧で打錠すると変性又は失活する化合物の粉粒体を含む錠剤を、工業的生産ベースで製造することができる。

請求項８に記載の錠剤の製造方法は、請求項３又は請求項４に記載の錠剤の製造方法の、杵と臼とを散布室内に収容する工程、散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、杵の表面及び前記臼の表面に滑沢剤を塗布する工程、及び、滑沢剤が表面に塗布された杵と、滑沢剤が表面に塗布された臼とを用いて、成形材料を打錠する工程を、連続して行うことを特徴とする。

この錠剤の製造方法では、打錠工程において、スティッキング等が生じないことを利用して、連続打錠するようにしているので、固体分散体粉粒体を含む錠剤を、工業的生産ベースで製造することができる。

請求項９に記載の錠剤の製造方法は、請求項１～８のいずれかに記載の錠剤の製造方法の、滑沢剤が表面に塗布された杵と、滑沢剤が表面に塗布された臼とを用いて、成形材料を打錠する工程の打錠圧が、低圧であることを特徴とする。

ここに、「低圧」は、従来の内部滑沢法や、従来の外部滑沢法に比べ、打錠圧

が低いことを意味する。より具体的に説明すると、この錠剤の製造方法は、１トン（ｔｏｎ）／ｃｍ^{2}未満の打錠圧を用いても、十分に、実用レベルの硬度を有する錠剤を製造できる。

この錠剤の製造方法では、成形材料を打錠する工程の打錠圧を、低圧にしているので、錠剤中に含ませる顆粒が、高圧で打錠すると変性又は失活する化合物の粉粒体を含む粉粒体材料であっても、そのような化合物変性又は失活させることなく、錠剤化できる。

また、錠剤中に含ませる顆粒が、固体分散体粉粒体であっても、固体分散体粉粒体の機能を破壊することなく、錠剤化できる。

請求項１０に記載の錠剤は、賦形剤中に、有効成分を含有する顆粒を含み、錠剤本体の表面にのみ滑沢剤を有し、且つ、顆粒が、高圧で打錠すると変性又は失活する化合物の粉粒体材料である。

この錠剤は、錠剤本体の表面にのみ滑沢剤を有するので、滑沢剤の撥水性等が原因となる錠剤の崩壊時間の遅れが生じない。

また、この錠剤では、錠剤内部に滑沢剤を含ませていないので、打錠圧を低くして打錠することができ、顆粒を構成する高圧で打錠すると変性又は失活する化合物の粉粒体材料が、変性したり又は失活したりすることがない。

請求項１１に記載の錠剤は、賦形剤中に、有効成分を含有する顆粒を含み、錠剤本体の表面にのみ滑沢剤を有し、且つ、顆粒が、固体分散体粉粒体である。

この錠剤は、錠剤本体の表面にのみ滑沢剤を有するので、滑沢剤の撥水性等が原因となる錠剤の崩壊時間の遅れが生じない。

また、この錠剤では、錠剤内部に滑沢剤を含ませていないので、打錠圧を低くして打錠できるため、固体分散体粉粒体の機能が損なわれていない。

請求項１２に記載の錠剤は、請求項１０又は請求項１１に記載の錠剤の、滑沢剤の使用量が、一錠剤当り、０．０００１重量％以上０．２重量％以下とされている。

この錠剤では、錠剤の表面に滑沢剤が微量しか存在しないので、滑沢剤の持つ撥水性が原因して、錠剤の崩壊時間が遅延するという問題が生じない。

従って、この錠剤（素錠）は、裸錠として用いれば、速溶錠となるので、口腔

内速溶錠のように、目的とする部位で、直ちに、錠剤が崩壊することが要求される錠剤として適しており、また、表面に、目的の部位で溶けるフィルムコートを施せば、フィルムコートが溶けると、錠剤本体も、直ちに、目的の部位で溶けるので、目的の部位で溶けることが要求される錠剤として好適に用いることができる。

請求項１３に記載の錠剤は、請求項１０～１２のいずれかに記載の錠剤の錠剤本体の形状が、異形であることを特徴とする。

ここに、本明細書で用いる「異形」は、錠剤の円形以外の形状を意味し、例えば、トラック型（カプセル型）や、ラグビーボール型や、３角形型、４角形型、５角形型その他の多角形型や、ダイヤモンド型、アーモンド型、砲弾型、半月型、ハート型、星型などの形状を意味する。

この錠剤は、錠剤本体の形状を異形にしているので、この形状から容易に錠剤内に含まれる薬剤（有効成分）を識別できる。このため、この錠剤は、投薬ミスが発生する虞れが無い。

請求項１４に記載の錠剤は、請求項１０～１３のいずれかに記載の錠剤が、錠剤本体の表面に割線を有する。

この錠剤では、錠剤本体の表面に割線を設けているので、目的の部位で溶ける錠剤であって、分割可能な錠剤を、市場に供給することができる。

図面の簡単な説明

第１図は、本発明に係る錠剤の製造方法に用いる外部滑沢式打錠機の一例の要部を拡大して概略的に示す断面図である。

第２図は、第１図に示す外部滑沢式打錠機を概略的に示す断面図である。

第３図は、第１図に示す外部滑沢式打錠機の要部を概略的に示す図であり、図３（ａ）は、本発明に係る外部滑沢式打錠機の要部を概略的に示す断面図であり、また、図３（ｂ）は、空気脈動波発生装置を中心に示す概略的に示す断面図である。

第４図は、空気脈動波の具体例を示す説明図であり、図４（ａ）及び図４（ｂ）に、各々、負圧の空気脈動波の具体例を示す。

第５図は、本発明に係る錠剤の製造方法に用いる外部滑沢式打錠機の他の一例を概略的に示す図であり、図５（ａ）は、本発明に係る外部滑沢式打錠機の要部を概略的に示す断面図であり、また、図５（ｂ）は、空気脈動波発生装置を中心に示す概略的に示す断面図である。

第６図は、空気脈動波の具体例を示す説明図であり、図６（ａ）及び図６（ｂ）に、各々、正圧の空気脈動波の具体例を示す。

第７図は、実験例で製造した種々の形状の錠剤を概略的に説明する図であり、図７中、左欄に、各々の錠剤の概略的な平面図を、また、右欄に、各々の錠剤の概略的な側面図を示す。

第８図は、実験例で製造した種々の形状の錠剤を概略的に説明する図であり、図８中、左欄に、各々の錠剤の概略的な平面図を、また、右欄に、各々の錠剤の概略的な側面図を示す。

第９図は、実験例で製造した種々の形状の錠剤を概略的に説明する図であり、図９中、左欄に、各々の錠剤の概略的な平面図を、また、右欄に、各々の錠剤の概略的な側面図を示す。

第１０図は、実験例で製造した種々の形状の錠剤を概略的に説明する図であり、図１０中、左欄に、各々の錠剤の概略的な平面図を、また、右欄に、各々の錠剤の概略的な側面図を示す。

第１１図は、実験例で製造した種々の形状の錠剤を概略的に説明する図であり、図１１中、左欄に、各々の錠剤の概略的な平面図を、また、右欄に、各々の錠剤の概略的な側面図を示す。

第１２図は、ホッパー内に収容された離型剤を導管内に定量的に供給する装置（定量フィーダ）を概略的に示す断面図である。

第１３図は、図１２に示す装置（定量フィーダ）に用いられている弾性体膜の一例を概略的に示す平面図である。

第１４図は、図１２に示す装置（定量フィーダ）の動作を概略的に説明する説明図である。

第１５図は、図１２に示す装置（定量フィーダ）に用いられている弾性体膜の他の一例を概略的に示す平面図である。

第１６図は、空気脈動波発生装置の他の一例を概略的に示す断面図である。

第１７図は、特公昭４１－１１２７３号公報に記載の、従来の錠剤の製造方法を概略的に示す工程図である。

第１８図は、特公昭５６－１４０９８号公報に記載の、従来の錠剤の製造方法を概略的に示す工程図である。

発明を実施するための最良の形態

以下に、本発明に係る錠剤の製造方法について、図面を参照しながら、更に詳しく説明する。

ここでは、ロータリ型錠剤機を用いた場合を例にして、本発明について説明する。

図１は、本発明を実施するために使用したロータリ型錠剤機の回転テーブルを中心に、その一部を拡大して概略的に示す構成図である。

また、図２は、図１に示す回転テーブルを中心に、その一部を拡大して概略的に示す断面図である。

このロータリ型錠剤機Ａは、図１及び図２に示すように、回転可能に設けられ、且つ、円周方向に複数の臼１、・・・が設けられた回転テーブル２と、回転テーブル２に設けられた複数の臼１、・・・に対応して設けられた、複数の上杵３、・・・及び下杵４、・・・とを備えている。そして、臼１内に成形材料を充填する位置Ｐ２の前段位置Ｐ１には、散布室８が設置されており、散布室８には、空気脈動波発生装置７が接続され、且つ、散布室８内には、滑沢剤Ｌを噴射する噴射用ノズル９が設置された構成となっている。この例では、噴射用ノズル９には、圧縮空気を充填したボンベのような空気源１０が接続されており、空気源１０より発生させた空気により、噴射用ノズル９から滑沢剤Ｌが噴霧されるようにしてある。

次に、この装置Ａを使用して、錠剤を製造する工程について説明する。

まず、回転テーブル２を所定の速度で回転し、回転テーブル２の回転に伴って、散布室８が設置された位置Ｐ１にきた臼１に、空気脈動波発生装置７を駆動して、散布室８内に空気脈動波を発生させるとともに、噴射用ノズル９から滑沢剤Ｌを

噴霧して、臼１の内周面１ｓ、上杵３の下端面３ｓ、及び、下杵４の上端面４ｓに滑沢剤Ｌを塗布する。

次に、回転テーブル２の回転に伴って、臼１内に成形材料ｍを充填する位置Ｐ２にきた臼１に成形材料ｍを充填し、余分な成形材料ｍをすりきりした後、成形材料ｍが充填された臼１が、成形材料ｍを圧縮して錠剤を製造する位置Ｐ３にきたときに、下端面３ｓに滑沢剤Ｌが塗布された上杵３と、上端面４ｓに滑沢剤Ｌが塗布された下杵４とにより、成形材料ｍを圧縮して錠剤を製造し、更に、臼１が、位置Ｐ４にきた時に、臼１内から錠剤Ｔを排出して、錠剤Ｔを製造する。

図３（ａ）は、散布室８の構成を中心に示す概略的な構成図であり、図３（ｂ）は、空気脈波発生装置７を例示的に示す構成図である。

この例では、空気脈動波発生装置７は、導管１３を介して散布室８に接続されている。

また、図３（ｂ）中、７１はブロアーを、７２は円筒型の筒体を、７３は筒体７２内に回転軸７４を中心にして、回転可能に、且つ、筒体７２内を２分割するように設けられた弁体を、各々示す。筒体７２の側面には、所定の位置に、導管１３と、ブロアー７１に連結される導管１４とが接続されている。そして、弁体７３は、弁体回転制御装置（図示せず。）により、所望の回転速度で回転できるようになっている。

ブロアー７１を所定の回転数で回転させるとともに、弁体７３を所定の回転速度で回転すると、図３（ｂ）中、弁体７３が、実線で示される位置にある時は、散布室８とブロアー７１とが連通状態になり、また、弁体７３が、想像線で示される位置にある時は、散布室８とブロアー７１との間が弁体７３により遮断された状態になり、例えば、図４（ａ）に示すような、山が大気圧で、谷が負の圧力の空気脈動波を散布室８内に発生させたり、また、図４（ｂ）に示すような、山と谷とがともに負の圧力の空気脈動波を散布室８内に発生させることができる。

ここで、「負の圧力」とは、散布室８内の圧力が、散布室８外の圧力（大気圧）より低くなっていることを意味する。

この錠剤の製造方法では、成形材料ｍ中には、滑沢剤Ｌを含んでいないため、打錠圧を１トン（ｔｏｎ）／ｃｍ^{2}以下としても、製造される錠剤に実用的な硬度

が得られるので、高圧で打錠すると変性又は失活する化合物を含有する錠剤や、固体分散体粉粒体を含有する錠剤を製造するのに適している。

且つ、散布室８内に、図４（ａ）または図４（ｂ）に示すような、空気脈動波を発生した状態で、噴射用ノズル９より滑沢剤Ｌを噴霧すると、噴霧された滑沢剤Ｌは、空気脈動波により拡散し、散布室８内に収容された臼１の内周面１ｓ、散布室８内に収容された臼１に対応して設けられた上杵３の下端面３ｓや、及び、下杵４の上端面４ｓに均一に塗布される。

即ち、この錠剤の製造方法では、臼１の内周面１ｓ、上杵３の下端面３ｓや、及び、下杵４の上端面４ｓに均一に滑沢剤Ｌを塗布できるために、散布室８内に噴霧する滑沢剤Ｌは、極めて微量であっても、成形材料ｍが、打錠機Ａの臼１、上杵３及び下杵４に付着するのを防止できる。

このことを利用して、散布室８内に噴霧する滑沢剤Ｌの噴霧量を、一錠剤の重量当り、０．０００１重量％以上０．２重量％以下となるように調整すれば、製造される錠剤Ｔは、その表面にのみ、臼１の内周面１ｓ、上杵３の下端面３ｓ及び下杵４の上端面４ｓに塗布されていた滑沢剤Ｌの一部が僅かに付着しているだけとなり、錠剤Ｔの内部には、滑沢剤Ｌを殆ど含まない錠剤が製造できる。

この結果、製造される錠剤Ｔは、従来の製造方法により製造された錠剤に比べ、錠剤Ｔ中に含まれる滑沢剤Ｌの使用量が著しく少ないので、従来の錠剤に見られたような滑沢剤Ｌの撥水性が原因して錠剤の崩壊時間が遅延するという問題が一切生じない。

従って、この錠剤の製造方法に従って製造される錠剤（素錠）Ｔは、裸錠として用いれば、速溶錠となるので、口腔内速溶錠のように、目的とする部位で、直ちに、錠剤が崩壊することが要求される錠剤として適している。

また、表面に、目的の部位で溶けるフィルムコートを施せば、フィルムコートが溶けると、錠剤本体も、直ちに、目的の部位で溶けるので、目的の部位で溶ける錠剤を製造することができる。

尚、この例では、空気脈動波発生装置７として、図３（ｂ）に示したような装置を用いた例を示したが、これは、単に、例示であって、空気脈動波発生装置７としては、種々のものを用いることができる。例えば、導管１３の終端にブロア

ー７１を接続するとともに、導管１３の途中に、導管１３を開閉する電磁弁を設け、ブロアー７１を所定の回転数で回転させて吸引するとともに、電磁弁により、導管を所定の周期で開閉してもよく、また、導管１３の終端にブロアー７１を接続し、ブロアー７１を所定の周期で速く回転させたり、遅く回転させるようにして、散布室８内の空気を所定の周期で、強く吸引したり弱く吸引したりしてもよい。

また、上記した例では、散布室８内に、図４（ａ）または図４（ｂ）に示すような、空気脈動波を発生させた例を示したが、図５に示すような装置を構成し、散布室８内に図６（ａ）または図６（ｂ）に示すような空気脈動波を発生させるようにしてもよい。即ち、図５に示す例では、図５（ａ）に示すように、導管１３の終端に、空気脈動波発生装置７Ａを接続し、導管１３の途中に、滑沢剤Ｌを貯留したホッパー１５を接続し、ホッパー１５には、圧縮空気が充填されたボンベ等の圧縮空気発生手段１６を接続している。尚、図５（ａ）中、１７で示す装置は、必要により設けられるブロアーを示しており、ブロアー１７を駆動させると、散布室８内の空気を吸引し、散布室８内に送り込まれた空気脈動波及び滑沢剤Ｌが散布室８から排出が促されるようになっている。

空気脈動波発生装置７Ａは、図５（ｂ）に示すように、ブロアー７１と、導管１３のブロアー７１とホッパー１５が接続される位置との間に接続された円筒型の筒体７２と、筒体７２内に回転軸７４を中心にして、回転可能に、且つ、筒体７２内を２分割するように設けられた弁体７３とを備える。筒体７２の側面には、所定の位置に、導管１３と、ブロアー７１に連結される導管１４とが接続されている。そして、弁体７３は、弁体回転制御装置（図示せず。）により、所望の回転速度で回転できるようになっている。

ブロアー７１を所定の回転数で回転させて、散布室８へ送風するとともに、弁体７３を所定の回転速度で回転すると、図５（ｂ）中、弁体７３が、実線で示される位置にある時は、散布室８とブロアー７１とが連通状態になり、また、弁体７３が、想像線で示される位置にある時は、散布室８とブロアー７１との間が弁体７３により遮断された状態になり、例えば、図６（ａ）に示すような、山が正の圧力で、谷が大気圧の空気脈動波を散布室８内に発生させたり、また、図６

（ｂ）に示すような、山と谷とがともに正の圧力の空気脈動波を散布室８内に発生させてもよい。そして、この状態を維持しつつ、圧縮空気発生手段１６を駆動させて、ホッパー１５内に収容された滑沢剤Ｌを導管１３へ送りだし、空気脈動波の流れに乗せて、所定量の滑沢剤Ｌを散布室８内へ送り込むようにしてもよい。

ここで、正の圧力とは、散布室８内の圧力が、散布室８外の圧力（大気圧）より高くなっていることを意味する。

また、導管１３の終端にブロアー７１を接続するとともに、導管１３の途中に、導管１３を開閉する電磁弁を設け、ブロアー７１を所定の回転数で回転させて散布室８へ空気を送風するとともに、電磁弁により、導管を所定の周期で開閉させて、空気脈動波を散布室８内及び導管１３内に発生させ、この状態を維持しつつ、圧縮空気発生手段１６を駆動させて、ホッパー１５内に収容された滑沢剤Ｌを導管１３へ送りだし、空気脈動波の流れに乗せて、所定量の滑沢剤Ｌを散布室８内へ送り込むようにしてもよく、また、導管１３の終端にブロアー７１を接続し、ブロアー７１を所定の周期で速く回転させたり、遅く回転させるようにして、散布室８内の空気を所定の周期で、散布室８へ空気を強く送風したり弱く送風し、空気脈動波を散布室８内及び導管１３内に発生させ、この状態を維持しつつ、圧縮空気発生手段１６を駆動させて、ホッパー１５内に収容された滑沢剤Ｌを導管１３へ送りだし、空気脈動波の流れに乗せて、所定量の滑沢剤Ｌを散布室８内へ送り込むようにしてもよい。

次に、具体的な実験データに基づいて、本発明を説明する。

（実験例１）

ここでは、高圧で打錠すると変性又は失活する化合物の粉粒体を含有する錠剤を製造した例を示す。

１０ｗ／ｖ％のセラペプチダーゼ水溶液に、１５ｗ／ｖ％乳糖水溶液を、セラペプチダーゼ１００ｇに対し、乳糖が５０ｇとなるように混合し、当初温度－５５℃、圧力10^{-3}ｍｍＨｇ、２７時間後の最終温度＋６０℃、圧力10^{-1}ｍｍＨｇ の条件下で乾燥凍結したものを、混合、練合、乾燥、整粒し、表１に、その処方を示す粉粒体（平均粒子径：６０μｍ）を準備した。

表１

配合成分	処方（ｍｇ）
セラペプチターゼ	５　ｍｇ
乳糖	８７　ｍｇ
コンスターチ	３７．５ｍｇ
イソプロパノール	０．０１５ｍｌ

次に、図１に示したような空気脈動波発生装置７を備えるロータリ型錠剤機Ａを使用して、整粒した造粒物が１３０ｍｇ／錠剤となるように、直径が、７ｍｍの杵臼セットを用いて、１分間に回転テーブル２を３０回転させる速度で、連続打錠した。

滑沢剤として、ステアリン酸マグネシウムを使用し、散布室内に噴霧するステアリン酸マグネシウムの使用量を、製造される一錠剤当りに含まれる滑沢剤の重量％が、０．０３重量％となるように調整した。

尚、打錠機Ａの本体としては、畑製作所製ＨＡＴＡ　ＨＴ－Ｘ２０を使用した。

図１に示したような空気脈動波発生装置７を備えるロータリ型錠剤機Ａを使用した場合、打錠圧は、０．７トン（ｔｏｎ）／ｃｍ^{2}で、製造される錠剤に実用的な硬度が得られることが判った。

尚、空気脈動波の条件は、特に限定されることはないが、この例では、空気脈動波の周期は、１Ｈｚ以上１０Ｈｚ以下とし、外気圧に対し、谷が、１０％～５％程度低い圧になるように、且つ、山が、外気圧とほぼ等しいか、これよりやや低い圧となる条件で行った。

また、空気脈動波の条件は、特に限定されることはないが、この例では、空気脈動波の周期は、１Ｈｚ以上１０Ｈｚ以下とし、外気圧に対し、谷が、１０％程度低い圧になるように、且つ、山が、外気圧とほぼ等しいか、これよりやや低い圧となる条件で行った。

（比較例１）

実験例１で用いた表１に示す処方の粉粒体材料に、滑沢剤として、ステアリン酸マグネシウムを使用し、一錠剤の全重量に対し、ステアリン酸マグネシウムが、

０．８重量％となるように添加し、Ｖ型混合機を用いて良く混合した後、この成形材料を１３０ｍｇ／錠剤となるように、直径が７ｍｍの杵臼セットを用いて、１分間に回転テーブルを３０回転させる速度で、内部滑沢法により、連続して、錠剤を打錠した。

打錠機としては、畑製作所製ＨＡＴＡ　ＨＴ－Ｘ２０を使用した。

この場合、打錠圧は、０．７トン（ｔｏｎ）／ｃｍ^{2}では、製造される錠剤に実用的な硬度が得られないことが判った。

（比較例２）

実験例１で用いた表１に示す処方の粉粒体材料を１３０ｍｇ／錠剤となるように、実施例１と同様の、直径が、７ｍｍの杵臼セットを用い、この杵臼セットの杵の表面及び臼の表面に、特公昭４１－１１２７３号公報に記載の方法にしたがって、滑沢剤として、ステアリン酸マグネシウムを使用して、製造される一錠剤当りに対し、滑沢剤の重量％が、０．０３重量％となる量を付着させ、しかる後に、１分間に回転テーブルを３０回転させる速度で、連続して、錠剤を打錠した。

打錠機としては、畑製作所製ＨＡＴＡ　ＨＴ－Ｘ２０を使用した。

次に、実験例１、比較例１及び比較例２で得られた３種の錠剤を、各々、日本薬局方に準じた崩壊試験を所定の検体数（Ｎ＝５）で行った。

結果を表２に示す。

表２

	打錠圧 (ton/cm²)	硬度(kg)	崩壊時間（分）	
			平均値 (標準偏差)	実測値
実験例1	０．７	7	３．０ (±０．２)	３．０
				２．７
				２．９
				３．２
				３．１
比較例1	０．７	4	７．２ (±０．９)	７．２
				７．８
				８．３
				６．４
				６．２
比較例2	０．７	7	４．０ (±０．６)	４．１
				３．５
				３．３
				４．８
				４．５

表２より、実験例１は、比較例１に比べ、硬度が高く、比較例１、２に比べ、崩壊時間が短く、また、崩壊時間のバラツキも小さいことが、明らかとなった。

（比較例３）

実験例１で用いた表１に示す処方の粉粒体材料に、滑沢剤として、ステアリン酸マグネシウムを使用し、一錠剤の全重量に対し、ステアリン酸マグネシウムが、０．８重量％となるように添加し、Ｖ型混合機を用いて良く混合した後、この成形材料１３０ｍｇ／錠剤となるように、直径が７ｍｍの杵臼セットを用いて、１分間に回転テーブルを３０回転させる速度で、内部滑沢法により、連続して、錠剤を打錠した。

この場合、製造される錠剤の硬度が実用的な硬度となるように、打錠圧は、１．

３トン（ｔｏｎ）／ｃｍ^{2}とした。

次に、実験例１、比較例２及び比較例３について、セラペプチダーゼの残存率を測定した所、残存率は、実験例１＞比較例２＞比較例３となった。

より具体的に説明すると、実験例１、比較例２及び比較例３で得たセラペプチダーゼを含有する錠剤を、４０℃で３カ月間保存した後、セラペプチダーゼの残存率を測定した所、実験例１の残存率は、９８．８％であったのに対し、比較例２は９０．７％であり、又、比較例３は８７．９％であり、このことより、本発明に従って製造されるセラペプチダーゼを含有する錠剤は、従来の製造方法により製造されるセラペプチダーゼを含有する錠剤に比べ、安定性が高いことが明らかになった。

また、実験例１と比較例１～３の各々について、５時間、連続打錠し、経時的に、得られた錠剤をサンプリングし、製造された錠剤の表面の滑らかさから、スティッキングを生じなかった時間を判定した所、実験例１は、５時間経過した時点でも、スティッキングを生じていなかったのに対し、比較例１、３は、１時間経過時点で、既に、スティッキングを生じており、また、比較例２は、２時間経過時点で、既に、スティッキングを生じていた。

以上の結果に基づけば、本発明に係る錠剤の製造方法を使用して製造した錠剤は、打錠圧を１トン（ｔｏｎ）／ｃｍ^{2}以下として製造（打錠）しても、実用的な硬度が得られる。このため、本発明に係る錠剤の製造方法を、高圧で打錠すると、安定性に問題がある（例えば、活性が低下する等の問題がある）薬物を含む錠剤を製造する際に用いれば、本発明に係る錠剤の製造方法により製造される錠剤は、従来の製造方法によって製造された錠剤に比べて、錠剤中に含有されている薬物の安定性を高くできる（例えば、錠剤中に含有される薬物の活性が低下する等の問題が生じない。）と考えられる。

従って、例えば、表３～表５に示す種々の薬物を含有する錠剤を製造する際に、本発明に係る錠剤の製造方法は、有効であることが示唆される。

表3

1. 解熱、鎮痛、消炎剤	インドメタシン、ジクロフェナックナトリウム、イブプロフェン、アスピリン、デキサメタゾン、プレドニゾロン、ロキソプロフェンナトリウム、ケトプロフェン、セラペプターゼ、塩化リゾチーム、ストレプトキナーゼ、サリチルアミド
2. 制酸、抗潰瘍剤	ファモチジン、スクラルファート、シメチジン、アセグルタミドアルミニウム、水酸化アルミニウムゲル、炭酸水素ナトリウム、ジアスターゼ、銅クロロフィリンナトリウム、エルーグルタミン、アルギン酸ナトリウム
3. 高血圧症、狭心症治療剤	塩酸ベニジピン、ニフェジピン、塩酸ニカルジピン、ベジル酸アムロジピン
4. 抗生物質	アモキシシリン、アンピシリン、塩酸ミノサイクリン
5. 鎮咳、抗喘息、気管支拡張剤	テオフィリン、塩酸メチルエフェドリン、クロモグリク酸ナトリウム、硫酸サルブタモール、リン酸コデイン
6. 利尿剤	フロセミド、フロロチアジド、スピロノラクトン
7. トランキライザー	ジアゼパム、クロルプロマジノン、ハロペリドール、ブロムペリドール、リスペリドン
8. 痛風治療剤	アロプリノール、プロベネシド
9. 血液凝固阻止剤	ワルファリンカリウム、ヘパリンナトリウム、アルテプラーゼ、ウロキナーゼ、チソキナーゼ
10. 血液凝固剤	血液凝固第8因子、活性化プロトロンビン複合体
11. エリスロポエチン製剤	エポエチンベータ、エポエチンアルファ
12. コレステロール及び脂質減少剤	プラバスタチンナトリウム、シンバスタチン、ベザフィブラート、ニコチン酸トコフェロール、デキストラン硫酸
13. 脳血管、抹消血管拡張剤	ニセルゴリン、イブジラスト、シチコリン、塩酸フルナリジン
14. カルシトニン製剤	エルカトニン、合成サケカルシトニン
15. 抗てんかん剤	フェニトイン、バルプロ酸ナトリウム、カルバマゼピン、ゾニサミド

表4

16.消化管運動機能調整剤	メトクロプラミド、ドンペリドン、シサプリド
17.去痰剤	塩酸ブロムヘキシン、カルボシステイン、塩酸エチルシステイン、塩酸アンブロキソール
18.糖尿病治療剤	グリベングラミド、トルブタミド、インスリン、グルカゴン様インスリノトロピックブペチド
19.循環器用剤	ユビデカレノン、ＡＴＰ－２ナトリウム、ニトログリセリン、２硝酸イソソルビド
20.ビタミン剤	ビタミンA、ビタミンB類、ビタミンC、ビタミンD、葉酸
21.濒尿治療剤、抗利尿ホルモン剤	塩酸フラボキサート、塩酸オキシブチニン、酢酸デスモプレシン、バソプレシン
22.アンギオテンシン変換酵素阻害剤	マレイン酸エナラプリル、アラセプリル
23.パーキンソン氏病治療剤	ドロキシドパ、メシル酸ペルゴリド、レボドパ、カルビドパ
24.消化剤	膵臓消化酵素配合剤、サナクターゼ配合剤、胃粘膜抽出製剤、チラクターゼ
25.制癌剤	テガフール、フルオロウラシル、ドキシフルリジン、メトトレキサート、エトポシド、硫酸ビンデシン、塩酸エピルビシン、エルーアスパラギナーゼ、酢酸リューブロレイン、酢酸ゴセレリン、酢酸クロルマジノン、クエン酸タモキシフェン、フィルグラスチム、レノグラスチム、ナルトグラスチム、レンチナン、インターフェロン
26.免疫抑制剤	シクロスポリン、ミゾリビン、免疫グロブリン
27.鎮痛剤	塩酸リドカイン、塩酸ブロカイン、硫酸モルヒネ、塩酸ブプレノルフィン、ペンタゾシン、フェンタニル
28.催眠鎮静剤	ブロチゾラム、トリアゾラム、フルニトラゼパム、塩酸フルラゼパム
29.向知能薬	イデベノン、プロベントフィリン、塩酸インデロキサジン、塩酸ビフェメラン

表5

30.抗アレルギー剤	プロピオン酸ベクロメタゾン、フマル酸ケトチフェン、アンレキサノクス、テルフェナジン、塩酸アゼラスチン、トラニラスト、オロパタジン、オキサトミド、塩酸エピナスチン、アステミゾール
31.診断用検査試薬、その他	13炭素尿素、グルカゴン、デンプン部分加水分解物、プロスタグランジン、ロイコトリエン、トロンボキサンA2、血小板活性化因子、インスリン様成長因子、神経成長因子、上皮細胞増殖因子、血管新生因子、リボ核酸、デオキシリボ核酸、オリゴヌクレオチド、トレハロース、デキストラン、キチン、アラビアゴム、寒天、コンドロイチン硫酸、ヒアルロン酸、シクロデキストリン、ベータグルカン、トリプシン、キモトリプシン、ペプシン、アプロチニン、ベスタチン、おたふく風邪ワクチン、ポリオワクチン、

また、製造される錠剤に、スティッキング等が生じ難いことも明らかになった。

（実験例2）

ここでは、固体分散体の粉粒体を含有する錠剤を製造した例を示す。

ドンペリドンを粉砕した原末（平均粒子径：60μm）500gに対し、ヒドロキシプロピルメチルセルロースアセテートサクシネート（商品名：Aコート、AS－MP、信越化学工業社製）2500gを混合し、その後、小量の水を添加しながら、口径4mmφ×2のダイを装着した2軸型エクストルーダー（KEX－25：栗本鉄工所社製）を用いてバレル温度を100℃に設定し、200rpmの押し出し速度で成形処理を行い、固体分散体を得た。

次に、以上により得られた固体分散体をサンプルミル（形式：AP－S、細川鉄工所社製）を用いて微粉砕した。

次に、外部滑沢式打錠機Aを用いて、以上により得られた固体分散体粉粒体を、杵3、4と臼1とを散布室8内に収容し、散布室8内に、図4（a）に示すような空気脈動波を発生させて、杵3、4の表面3s、4s及び臼1の表面1sに、滑沢剤Lとして、ステアリン酸マグネシウムを塗布し、杵3、4の表面3s、4s及び臼1の表面1sに、ステアリン酸マグネシウムが塗布された、杵3、4及び臼1を用いて、顆粒を、1分間に回転テーブル2を30回転させる速度で、連

続して、打錠した。

空気脈動波の条件は、特に限定されることはないが、この例では、空気脈動波の周期は、１Ｈｚ以上１０Ｈｚ以下とし、外気圧に対し、谷が、１０％程度低い圧になるように、且つ、山が、外気圧とほぼ等しいか、これよりやや低い圧となる条件で行った。

次に、以上により得られた固体分散体の錠剤の溶解度試験と、この錠剤を粉砕し、粉末Ｘ線回折（２５０メッシュ通過）とを行った。

（比較例４）

ドンペリドンを粉砕した原末（平均粒子径：６０μｍ）５００ｇに対し、ヒドロキシプロピルメチルセルロースアセテートサクシネート（商品名：Ａコート、ＡＳ－ＭＰ、信越化学工業社製）２５００ｇを混合し、その後、小量の水を添加しながら、口径４ｍｍφ×２のダイを装着した２軸型エクストルーダー（ＫＥＸ－２５：栗本鉄工所社製）を用いてバレル温度を１００℃に設定し、２００ｒｐｍの押し出し速度で成形処理を行い、固体分散体を得た。

次に、以上により得られた固体分散体をサンプルミル（形式：ＡＰ－Ｓ、細川鉄工所社製）を用いて微粉砕し、得られた微粒子の溶解度試験と、粉末Ｘ線回折（２５０メッシュ通過）とを行った。

その結果、実験例２と比較例４とは、ほぼ同じ溶解度を示し、且つ、ともに、ドンペリドンの結晶ピークが消滅していることが明らかになった。

また、実験例２と比較例４の各々について、５時間、連続打錠し、経時的に、得られた錠剤をサンプリングし、製造された錠剤の表面の滑らかさから、スティッキングを生じなかった時間を判定した所、実験例２は、５時間経過した時点でも、スティッキングを生じていなかったのに対し、比較例４は、１時間経過時点で、既に、スティッキングを生じていた。

以下、表３～表５に示す種々の薬物について、２軸型エクストルーダーを用いて、種々の固体分散体を製造し、実験例２と比較例４と同様の試験を行ったが、外部滑沢式打錠機Ａを用い、杵３、４と臼１とを散布室８内に収容し、散布室８内に、図４（ａ）に示すような空気脈動波を発生させて、杵３、４の表面３ｓ、４ｓ及び臼１の表面１ｓに、滑沢剤Ｌを塗布し、杵３、４の表面３ｓ、４ｓ及び

臼１の表面１ｓに、ステアリン酸マグネシウムが塗布された、杵３、４及び臼１を用いて、顆粒を、１分間に回転テーブル２を３０回、回転させる速度で、連続打錠した錠剤と、固体分散体をサンプルミルを用いて微粉砕して得られた微粒子とは、各々、互いに、ほぼ同じ溶解度を示し、且つ、ともに、薬物の結晶ピークが消滅していることが明らかになった。

以上の結果から、本発明に係る錠剤の製造方法は、固体分散体の錠剤を製造する際に、好適に用いることができることが、明らかになった。

次に、図７～図１１の各々に示す錠剤の雌型を構成する杵と臼とを用いる以外は、実験例１、実験例２と同様にして、種々の異形錠剤を作製した。

ここに、図７（ａ）に示す錠剤は、一般に、フラット　プレイン（ＦＬＡＴ　ＰＬＡＩＮ）と呼ばれる円形状の錠剤を示し、図７（ｂ）に示す錠剤は、一般に、シャロウ　コンケーブ　プレイン（ＳＨＡＬＬＯＷ　ＣＯＮＣＡＶＥ　ＰＬＡＩＮ）と呼ばれる円形状の錠剤を示し、図７（ｃ）に示す錠剤は、一般に、ノーマル　コンケーブ　プレイン（ＮＯＲＭＡＬ　ＣＯＮＣＡＶＥ　ＰＬＡＩＮ）と呼ばれる円形状の錠剤を示し、図７（ｄ）に示す錠剤は、一般に、ディープ　コンケーブ　プレイン（ＤＥＥＰ　ＣＯＮＣＡＶＥ　ＰＬＡＩＮ）と呼ばれる円形状の錠剤を示し、図７（ｅ）に示す錠剤は、一般に、ボール又はピル（ＢＡＬＬ　ＯＲ　ＰＩＬＬ）と呼ばれる円形状の錠剤を示し、又、図７（ｆ）に示す錠剤は、一般に、フラット　ビベリッド　エッジ（ＦＬＡＴ　ＢＥＶＥＬＬＥＤ　ＥＤＧＥ）と呼ばれる円形状の錠剤を示している。

また、図８（ａ）に示す錠剤は、一般に、ダブル　ラディアス（ＤＯＵＢＬＥ　ＲＡＤＩＵＳ）と呼ばれる円形状の錠剤を示し、図８（ｂ）に示す錠剤は、一般に、ビベル　アンド　コンケーブ（ＢＥＶＥＬ　ＡＮＤ　ＣＯＮＣＡＶＥ）と呼ばれる円形状の錠剤を示し、図８（ｃ）に示す錠剤は、一般に、ディンプル（ＤＩＭＰＬＥ）と呼ばれる円形状の錠剤を示し、図８（ｄ）に示す錠剤は、一般に、リング（ＲＩＮＧ）と呼ばれる円形状の錠剤を示し、図８（ｅ）に示す錠剤は、一般に、リム（ＲＩＭ）と呼ばれる円形状の錠剤を示し、又、図８（ｆ）に示す錠剤は、一般に、カプセル（ＣＡＰＳＵＬＥ）と呼ばれるカプセル形状の錠剤を示している。

また、図９（ａ）に示す錠剤は、一般に、オーバル（ＯＶＡＬ）と呼ばれる楕円形状の錠剤を示し、図９（ｂ）に示す錠剤は、一般に、エリプス（ＥＬＬＩＰＳＥ）と呼ばれる楕円形状の錠剤を示し、図９（ｃ）に示す錠剤は、一般に、スクエア（ＳＱＵＡＲＥ）と呼ばれる四角形状の錠剤を示し、図９（ｄ）に示す錠剤は、一般に、トライアングル（ＴＲＩＡＮＧＬＥ）と呼ばれる三角形状の錠剤を示し、図９（ｅ）に示す錠剤は、一般に、ペンタゴン（ＰＥＮＴＡＧＯＮ）と呼ばれる五角形状の錠剤を示し、又、図９（ｆ）に示す錠剤は、一般に、ヘキサゴン（ＨＥＸＡＧＯＮ）と呼ばれる六角形状の錠剤を示している。

また、図１０（ａ）に示す錠剤は、一般に、ヘプタゴン（ＨＥＰＴＡＧＯＮ）と呼ばれる七角形状の錠剤を示し、図１０（ｂ）に示す錠剤は、一般に、オクタゴン（ＯＣＴＡＧＯＮ）と呼ばれる八角形状の錠剤を示し、図１０（ｃ）に示す錠剤は、一般に、ダイヤモンド（ＤＩＡＭＯＮＤ）と呼ばれるダイヤモンド形状の錠剤を示し、図１０（ｄ）に示す錠剤は、一般に、ピロウ又はバレル（ＰＩＬＬＯＷ　ＯＲ　ＢＡＬＬＥＬ）と呼ばれる枕形状の錠剤を示し、図１０（ｅ）に示す錠剤は、一般に、レクタングル（ＲＥＣＴＡＮＧＬＥ）と呼ばれる方形状の錠剤を示し、又、図１０（ｆ）に示す錠剤は、一般に、アーモンド（ＡＬＭＯＮＤ）と呼ばれるアーモンド形状の錠剤を示している。

また、図１１（ａ）に示す錠剤は、一般に、アロウ　ヘッド（ＡＲＲＯＷ　ＨＥＡＤ）と呼ばれる鏃形状の錠剤を示し、図１１（ｂ）に示す錠剤は、一般に、バレット（ＢＵＬＬＥＴ）と呼ばれる砲弾形状の錠剤を示し、図１１（ｃ）に示す錠剤は、一般に、ハーフ　ムーン（ＨＡＬＦ　ＭＯＯＮ）と呼ばれる半月形状の錠剤を示し、図１１（ｄ）に示す錠剤は、一般に、シェルド（ＳＨＥＬＤ）と呼ばれる貝殻形状の錠剤を示し、図１１（ｅ）に示す錠剤は、一般に、ハート（ＨＥＡＲＴ）と呼ばれるハート形状の錠剤を示し、又、図１１（ｆ）に示す錠剤は、一般に、スター（ＳＴＡＲ）と呼ばれる星形状の錠剤を示している。

図７～図１１の各々に示す錠剤の雌型を構成する杵と臼とを各々用い、５時間、連続打錠し、経時的に、得られた錠剤をサンプリングし、製造された錠剤の表面の滑らかさから、スティッキングを生じた時間を判定した所、５時間後でも、スティッキングを生じなかった。

以上の結果から、本発明に係る錠剤の製造方法は、円形錠剤を製造する場合のみならず、異形錠剤を製造する際にも、好適に用いることができることが、明らかになった。

また、刻印や割線を有する錠剤についても、実験例１、実験例２とは、上杵として、割線を形成する突条を有するものを用いる以外は同様にして、種々の分割錠剤を作製した。

５時間、連続打錠し、経時的に、得られた錠剤をサンプリングし、製造された錠剤の表面の滑らかさから、スティッキングを生じた時間を判定した所、５時間後でも、スティッキングを生じなかった。

尚、上記した実験例では、いずれも、負の空気脈動波を用いた例について説明したが、空気脈動波は、負の空気脈動波に限られず、正の空気脈動波を用いても、同様の結果を得ることができる。

この場合、正の空気脈動波の条件は、特に限定されることはないが、周期は、１Ｈｚ以上１０Ｈｚ以下とし、外気圧に対し、山が、１０％～５％程度高い圧になるように、且つ、谷が、外気圧とほぼ等しいか、これよりやや高い圧となる条件で行えば良い。

また、この発明の実施の形態では、図５に示したような、導管１３の途中に、ホッパー１５を接続し、ホッパー１５に、圧縮空気が充填されたボンベ等の圧縮空気発生手段１６を接続した装置を用いた例について説明したが、ホッパー１５内に貯留した滑沢剤Ｌを、導管１３に排出する装置は、このような装置に限定されることはない。

図１２は、そのような装置を概略的に説明する構成図である。

この装置は、導管１３の一端１３ａに、脈動空気振動波発生装置７Ａを接続し、導管１３の途中の位置に、ホッパー１５の排出口１５ａを接続し、この排出口１５ａに、ホッパー１５の底面をなすように、孔（この例では、スリット孔）１８ａを有する弾性体膜１８を設けている（図１３を参照）。

弾性体膜１８は、例えば、シリコーンゴム等のゴムで製されている。

尚、図１２中、１５ｂで示す部材は、蓋体を示しており、蓋体１５ｂは、ホッパー１５に対して着脱自在に、且つ、気密に取り付けられるようになっている。

次に、この装置の動作について説明する。

図１４は、この装置の動作を概略的に説明する説明図である。

この装置を使用する際には、ホッパー１５内に、滑沢剤Ｌを収容した後、ホッパー１５に蓋体１５ｂを気密に取り付ける。

次に、脈動空気振動波発生装置７Ａを駆動して、導管１３内に、正圧の空気脈動波を供給すると、導管１３内に供給された、正圧の空気脈動波が山側にある際には、ホッパー１５内の気圧に比べ、導管１３内の気圧が高くなり、図１４（ａ）に示すように、弾性体膜１８が、その中央部が腹になり、その周縁部が節になって、その中央部が上方に湾曲した形状になる。

この時、孔（この例では、スリット孔）１８ａは、その断面が、上側が開いたＶ字形状になる。そして、ホッパー１５内に貯留された滑沢剤Ｌの一部が、上側が開いたＶ字形状になった孔（この例では、スリット孔）１８ａ内に落下する。

次に、導管１３内に供給された、正圧の空気脈動波が山側から谷側に移行するにつれ、導管１３内の気圧が低くなり、導管１３内の気圧とホッパー１５内の気圧とが次第に等しくなり、この時、弾性体膜１８は、図１４（ｂ）に示すように、その復元力により元の状態に戻ろうとする。そして、この時、上側が開いたＶ字形状になった孔（この例では、スリット孔）１８ａ内に落下した滑沢剤Ｌが、孔（この例では、スリット孔）１８ａに挟み込まれた状態になる。

次に、導管１３内に供給された、正圧の空気脈動波が谷側にある際には、ホッパー１５内の気圧に比べ、導管１３内の気圧が低くなり、図１４（ｃ）に示すように、弾性体膜１８が、その中央部が腹になり、その周縁部が節になって、その中央部が下方に湾曲した形状になる。

この時、孔（この例では、スリット孔）１８ａは、その断面が、下側が開いた逆Ｖ字形状になる。そして、弾性体膜１８の孔（この例では、スリット孔）１８ａ内に挟み込まれていた滑沢剤Ｌが、導管１３内へと排出される。

そして、導管１３内に排出された滑沢剤Ｌは、導管１３内で、導管１３内に供給されている、正圧の空気脈動波に直ちに混和し、分散した状態となって、散布室（図５に示す散布室８を参照）へ気力輸送される。

ところで、弾性体膜１８は、正圧の空気脈動波の振幅、波長、波形、振動数等

に応じて、図１４（ａ）～図１４（ｃ）に示したような上下の振動を繰り返す。

従って、導管１３内に供給する正圧の空気脈動波の振幅、波長、波形、振動数等を一定にしている限り、弾性体膜１８は、一定の振幅、振動数で上下に振動することとなるため、孔（この例では、スリット孔）１８ａを介して、導管１３内へ排出される滑沢剤Ｌの量も一定になる。

且つ、この装置では、導管１３内に、正圧の空気脈動波を供給するようにしている結果、定常圧空気を用いて、粉体を気力輸送する場合に見られるような、導管１３の内壁面への粉体の付着現象や、導管１３内における粉体の吹き抜け現象が生じない。

従って、この装置は、弾性体膜１８の孔（この例では、スリット孔）１８ａを介して、導管１３内へ排出される滑沢剤Ｌが、導管１３内へ排出された時点における濃度と実質的に同じ濃度で、導管１３の他端１３ｂから排出される。

即ち、この装置は、定量フィーダ装置として機能する。

従って、この装置の導管１３の他端１３ｂを、散布室（図５に示す散布室８を参照）に接続すれば、孔（この例では、スリット孔）１８ａの大きさを一定にし、導管１３内へ供給する、正圧の空気脈動波の振幅、波長、波形、振動数等を一定にしている限り、散布室（図５に示す散布室８を参照）内に、常に、一定濃度の滑沢剤Ｌを供給することができる。

しかも、滑沢剤Ｌを気力輸送する媒体は、正圧の空気脈動波ではあるものの空気であるため、正圧の空気脈動波に混和させる滑沢剤Ｌを極めて微量にすることも可能である。

これにより、散布室（図５に示す散布室８を参照）内に、極めて微量の滑沢剤Ｌを、常に、安定した状態で噴霧できるため、散布室（図５に示す散布室８を参照）内に収容されている、杵の表面（図２に示す、上杵３の表面（下端面）３ｓ及び下杵４の表面（上端面）４ｓを参照）や、臼１の表面（内周面）１ｓに、極めて微量の滑沢剤Ｌを均一に塗布することができる。

尚、図１２では、弾性体膜として、スリット孔１８ａを有するものについて説明したが、これは、単に、好ましい例を示したに過ぎず、弾性体膜に設ける孔は、スリット孔１８ａに限られず、小孔であってもよく、且つ、そのような小孔は、

１個に限られることはない。そのような弾性体膜として、例えば、図１５に示すように、複数個の小孔１８ｂを有する弾性体膜を用いてもよい。

また、孔の大きさや、数を変えることや、導管１３内に供給する、正圧の空気脈動波の条件（振幅、波長、波形、振動数等）を変えれば、散布室（図５に示す散布室８を参照）内に噴霧する離型剤の濃度を種々の濃度に変えることができる。

また、この発明の実施の形態では、空気脈動波発生装置として、図３（ｂ）及び図５（ｂ）に示したような、筒体７２内に回転軸７４を中心にして、回転可能に、且つ、筒体７２内を２分割するように設けられた弁体７３を設けた、ロータリ型の空気脈動波発生装置７Ａについて説明したが、空気脈動波発生装置は、空気脈動波発生装置７Ａに限定されることはない。

図１６は、空気脈動波発生装置の他の一例を概略的に示す断面図である。

この高圧脈動空気発生器７Ｂは、入力ポート９１と出力ポート９２との間に弁座９３を設けた弁室９４に、カム機構９５によって開閉する弁体９６とを備える。

カム機構９５は、モーター等の駆動手段（図示せず）により回転可能に設けられた回転カム９７と、弁体９６の下端に取着されたローラ９８とを備える。

弁座９３は、出力ポート９２方向に先すぼんだ形状の孔部にされており、弁体９６は、弁座９３の形状に合わせた先すぼんだ逆すり鉢形状にされており、弁座９３を気密に塞ぐことができるようになっている。

また、この例では、弁体９６の軸部９６ａが、ケース体９９の軸孔９９ｈ内に、空気がもれないように、且つ上下に移動自在に設けられている。

ローラ９８は、回転カム９７に、回転可能に挟持され、回転カム９７を回転することで、回転カム９７に設けられた凹凸パターンに従って、回転しながら上下動するようになっている。

より詳しく説明すると、回転カム９７は、内側回転カム９７ａと外側回転カム９７ｂとを備えている。

内側回転カム９７ａ及び外側回転カム９７ｂの各々には、凹凸パターンが、ローラー９８の間隔を保持するように且つ互いに整列するように設けられている。

そして、ローラ９８は、内側回転カム９７ａと外側回転カム９７ｂとの間に挟持され、弁体９６にハネを生じることがなく、回転カム９７を回転させることで、

内側回転カム９７ａと外側回転カム９７ｂとに設けられた凹凸パターンに従って、回転しながら上下動するようになっている。

尚、この回転カム９７に設ける凹凸パターンは、ホッパー１５内に貯留する滑沢剤Ｌの物性に応じて、異なったパターンのものが選択される。

また、この例では、入力ポート９１に流量制御装置１０２が接続されており、入力ポート９１には、空気源７１で発生させ、流量制御装置１０２により所定の流量に調整された圧縮空気が供給されるようになっている。

また、出力ポート９２には、導管（図３又は図５に示す導管１３）の一端が接続されている。

尚、図５中、１００は、必要により設けられる、流量調整ポートを示しており、流量調整ポート１００には、出力ポート９２より出力する、空気脈動波の圧力を調整する出力調整弁１０１が、大気との完全な連通状態から遮断状態迄の間で所望の状態に調整可能に設けられている。

次に、この高圧脈動空気発生器７Ｂを用いて所望の周期、振幅及び波形を有する、正圧の空気脈動波を発生させる動作手順について説明する。

まず、ホッパー１５内に貯留する滑沢剤Ｌの物性に応じて、滑沢剤Ｌを空気に混和するのが容易な回転カム９７を高圧脈動空気発生器７Ｂの駆動手段（図示せず）の回転軸Ｍａに取り付ける。

次に、空気源７１を駆動し、流量制御装置１０２を調整することで、入力ポート９２に所定の流量の圧縮空気を供給する。

また、駆動手段（図示せず）を駆動することで、回転カム９７を所定の回転速度で回転させる。

また、必要により、出力調整弁１０１を調整することで、出力ポート９２より出力される空気脈動波の圧力を調整する。

回転カム９７を所定の回転速度で回転させると、弁体９６を回転カム９７に設けられた凹凸パターンに従って上下する。これにより、弁座９３を、例えば、回転カム９７に設けられた凹凸パターンに従って、全閉、半開、全開等に制御することで所望の波形の空気脈動波を出力ポート９２から出力する。

尚、この高圧脈動空気発生器７Ｂでは、出力ポート９２から出力する空気脈動

波の周期を所望の周期にするには、駆動手段（図示せず）を制御して、回転カム９７の回転速度を変えればよい。また、出力ポート９２から出力する空気脈動波の振幅を所望の振幅にするには、空気源７１、流量制御装置１０２及び／又は出力調整弁１０１を適宜調整すればよい。

産業上の利用可能性

以上、詳細に説明したように、請求項１に記載の錠剤の製造方法では、杵及び臼に、空気脈動波を発生させた散布室内に滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を空気脈動波に混和させて、塗布するようにしたので、従来の外部滑沢法に比べ、杵の表面及び臼の表面に、滑沢剤を均一に塗布できる。

この結果、高圧で打錠すると変性又は失活する化合物粉粒体を打錠する工程において、杵の表面及び臼の表面に、高圧で打錠すると変性又は失活する化合物粉粒体が付着し難くなり、製造される生物学的製剤の錠剤に、スティッキングや、キャッピングや、ラミネーティング等を生じ難い。

且つ、錠剤の表面に滑沢剤が付着しているに過ぎず、その内部には、滑沢剤が含まれていないため、滑沢剤を内部に含む錠剤に比べ、低い打錠圧（具体的には、１トン（ｔｏｎ）／ｃｍ^{2}未満の打錠圧）を用いて、高圧で打錠すると変性又は失活する化合物粉粒体を打錠しても、製造される錠剤は、実用レベルの硬度を有する。

請求項２に記載の錠剤の製造方法では、杵及び臼に、空気脈動波を発生させた散布室内に滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を空気脈動波に混和させて、塗布するようにしたので、従来の外部滑沢法に比べ、杵の表面及び臼の表面に、滑沢剤を均一に塗布できる。

この結果、固体分散体粉粒体を打錠する工程において、杵の表面及び臼の表面に、成形材料が付着し難くなり、製造される固体分散体の錠剤に、スティッキングや、キャッピングや、ラミネーティング等を生じ難い。

しかも、製造される固体分散体の錠剤は、その表面に滑沢剤が付着しているに過ぎず、その内部には、滑沢剤が含まれていないため、滑沢剤を内部に含む固体分散体の錠剤に比べ、低い打錠圧を用いて、固体分散体粉粒体を打錠しても、製

造される固体分散体の錠剤は、実用レベルの硬度を有する。

したがって、この錠剤の製造方法を用いれば、低い打錠圧で、固体分散体の錠剤を製造できるので、固体分散体の物性が変化することがない。

請求項３に記載の錠剤の製造方法では、散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を塗布するようにしたので、従来の外部滑沢法に比べ、杵の表面及び臼の表面に、滑沢剤を均一に塗布できる。

この結果、高圧で打錠すると変性又は失活する化合物粉粒体を打錠する工程において、杵の表面及び臼の表面に、高圧で打錠すると変性又は失活する化合物粉粒体が付着し難くなり、製造される生物学的製剤の錠剤に、スティッキングや、キャッピングや、ラミネーティング等を生じ難い。

且つ、錠剤の表面に滑沢剤が付着しているに過ぎず、その内部には、滑沢剤が含まれていないため、滑沢剤を内部に含む錠剤に比べ、低い打錠圧（具体的には、１トン（ｔｏｎ）／ｃｍ^{2}未満の打錠圧）を用いて、高圧で打錠すると変性又は失活する化合物粉粒体を打錠しても、製造される錠剤は、実用レベルの硬度を有する。

請求項４に記載の錠剤の製造方法では、散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、杵の表面及び臼の表面に、滑沢剤を塗布するようにしたので、従来の外部滑沢法に比べ、杵の表面及び臼の表面に、滑沢剤を均一に塗布できる。

この結果、固体分散体粉粒体を打錠する工程において、杵の表面及び臼の表面に、成形材料が付着し難くなり、製造される固体分散体の錠剤に、スティッキングや、キャッピングや、ラミネーティング等を生じ難い。

しかも、製造される固体分散体の錠剤は、その表面に滑沢剤が付着しているに過ぎず、その内部には、滑沢剤が含まれていないため、滑沢剤を内部に含む固体分散体の錠剤に比べ、低い打錠圧を用いて、固体分散体粉粒体を打錠しても、製造される固体分散体の錠剤は、実用レベルの硬度を有する。

したがって、この錠剤の製造方法を用いれば、低い打錠圧で、固体分散体の錠剤を製造できるので、固体分散体の物性が変化することがない。

請求項５に記載の錠剤の製造方法では、打錠する錠剤の一錠当りの使用量を、０．０００１重量％以上０．２重量％以下となるようにしたので、錠剤の崩壊時間が延長したり、硬度が低下したりしない。

請求項６に記載の錠剤の製造方法では、錠剤に割線を形成する突条を設けた杵を用いているので、高圧で打錠すると変性又は失活する化合物の粉粒体を含む分割可能錠剤や、機能が損なわれていない固体分散体粉粒体を含む分割可能錠剤を容易に製造することができる。

請求項７に記載の錠剤の製造方法では、打錠工程において、スティッキング等が生じないことを利用して、連続打錠するようにしているので、高圧で打錠すると変性又は失活する化合物の粉粒体を含む錠剤を、工業的生産ベースで製造することができる。

請求項８に記載の錠剤の製造方法では、打錠工程において、スティッキング等が生じないことを利用して、連続打錠するようにしているので、固体分散体粉粒体を含む錠剤を、工業的生産ベースで製造することができる。

請求項９に記載の錠剤の製造方法では、成形材料を打錠する工程の打錠圧を、低圧にしているので、錠剤中に含ませる顆粒が、高圧で打錠すると変性又は失活する化合物の粉粒体を含む粉粒体材料であっても、そのような化合物変性又は失活させることなく、錠剤化できる。

また、錠剤中に含ませる顆粒が、固体分散体粉粒体であっても、固体分散体粉粒体の機能を破壊することなく、錠剤化できる。

請求項１０に記載の錠剤は、錠剤本体の表面にのみ滑沢剤を有するので、滑沢剤の撥水性等が原因となる錠剤の崩壊時間の遅れが生じない。

また、この錠剤では、錠剤内部に滑沢剤を含ませていないので、打錠圧を低くして打錠しているので、顆粒を構成する高圧で打錠すると変性又は失活する化合物の粉粒体材料が、変性したり又は失活したりすることがない。

請求項１１に記載の錠剤は、錠剤本体の表面にのみ滑沢剤を有するので、滑沢剤の撥水性等が原因となる錠剤の崩壊時間の遅れが生じない。

また、この錠剤では、錠剤内部に滑沢剤を含ませていないので、打錠圧を低くして打錠しているので、固体分散体粉粒体の機能が損なわれていない。

請求項１２に記載の錠剤では、錠剤の表面に滑沢剤が微量しか存在しないので、滑沢剤の持つ撥水性が原因して、錠剤の崩壊時間が遅延するという問題が生じない。

従って、この錠剤（素錠）は、裸錠として用いれば、速溶錠となるので、口腔内速溶錠のように、目的とする部位で、直ちに、錠剤が崩壊することが要求される錠剤として適しており、また、表面に、目的の部位で溶けるフィルムコートを施せば、フィルムコートが溶けると、錠剤本体も、直ちに、目的の部位で溶けるので、目的の部位で溶けることが要求される錠剤として好適に用いることができる。

請求項１３に記載の錠剤は、錠剤本体の形状を異形にしているので、この形状から容易に錠剤内に含まれる薬剤（有効成分）を識別できる。このため、この錠剤は、投薬ミスが発生する虞れが無い。

請求項１４に記載の錠剤では、錠剤本体の表面に割線を設けているので、目的の部位で溶ける錠剤であって、分割可能な錠剤を、市場に供給することができる。

請求の範囲

1．成形材料を、杵と臼とを用いて圧縮成形して錠剤を製造する、錠剤の製造方法であって、

前記成形材料として、高圧で打錠すると変性又は失活する化合物の粉粒体を含む粉粒体材料を用い、

前記杵と前記臼とを散布室内に収容し、

前記散布室内に、空気脈動波を発生させるとともに、空気に混和した滑沢剤を噴霧し、前記散布室内に噴霧された滑沢剤を、前記空気脈動波に混和し、前記空気脈動波に混和した状態下で、前記杵の表面及び前記臼の表面に、前記滑沢剤を塗布し、

前記滑沢剤が表面に塗布された杵と、前記滑沢剤が表面に塗布された臼とを用いて、前記成形材料を打錠するようにした、錠剤の製造方法。

2．成形材料を、杵と臼とを用いて圧縮成形して錠剤を製造する、錠剤の製造方法であって、

前記成形材料として、固体分散体粉粒体を用い、

前記杵と前記臼とを散布室内に収容し、

前記散布室内に、空気脈動波を発生させるとともに、空気に混和した滑沢剤を噴霧し、前記散布室内に噴霧された滑沢剤を、前記空気脈動波に混和し、前記空気脈動波に混和した状態下で、前記杵の表面及び前記臼の表面に、前記滑沢剤を塗布し、

前記滑沢剤が表面に塗布された杵と、前記滑沢剤が表面に塗布された臼とを用いて、前記成形材料を打錠するようにした、錠剤の製造方法。

3．成形材料を、杵と臼とを用いて圧縮成形して錠剤を製造する、錠剤の製造方法であって、

前記成形材料として、高圧で打錠すると変性又は失活する化合物の粉粒体を含む粉粒体材料を用い、

前記杵と前記臼とを散布室内に収容し、

前記散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、前記杵の表

面及び前記臼の表面に、前記滑沢剤を塗布し、

前記滑沢剤が表面に塗布された杵と、前記滑沢剤が表面に塗布された臼とを用いて、前記成形材料を打錠するようにした、錠剤の製造方法。

4．成形材料を、打錠機の杵と臼とを用いて圧縮成形して錠剤を製造する、錠剤の製造方法であって、

前記成形材料として、固体分散体粉粒体を用い、

前記杵と前記臼とを散布室内に収容し、

前記散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、前記杵の表面及び前記臼の表面に、前記滑沢剤を塗布し、

前記滑沢剤が表面に塗布された杵と、前記滑沢剤が表面に塗布された臼とを用いて、前記成形材料を打錠するようにした、錠剤の製造方法。

5．前記散布室内に噴霧する滑沢剤の噴霧量を、一錠剤当り、0．0001重量%以上0．2重量%以下になるようにした、請求項1～4のいずれかに記載の錠剤の製造方法。

6．前記杵には、錠剤に割線を形成する突条が設けられている、請求項1～5のいずれかに記載の錠剤の製造方法。

7．前記杵と前記臼とを散布室内に収容する工程、前記散布室内に、空気脈動波を発生させるとともに、空気に混和した滑沢剤を噴霧し、前記散布室内に噴霧された滑沢剤を、前記空気脈動波に混和し、前記空気脈動波に混和した状態下で、前記杵の表面及び前記臼の表面に、前記滑沢剤を塗布する工程、及び、

前記滑沢剤が表面に塗布された杵と、前記滑沢剤が表面に塗布された臼とを用いて、前記成形材料を打錠する工程を、連続して行うことを特徴とする、請求項1又は請求項2に記載の錠剤の製造方法。

8．前記杵と前記臼とを散布室内に収容する工程、前記散布室内に、正圧の空気脈動波に混和した滑沢剤を噴霧して、前記杵の表面及び前記臼の表面に滑沢剤を塗布する工程、及び、前記滑沢剤が表面に塗布された杵と、前記滑沢剤が表面に塗布された臼とを用いて、前記成形材料を打錠する工程を、連続して行うことを特徴とする、請求項3又は請求項4に記載の錠剤の製造方法。

9．前記滑沢剤が表面に塗布された杵と、前記滑沢剤が表面に塗布された臼と

を用いて、前記成形材料を打錠する工程の打錠圧が、低圧であることを特徴とする、請求項１～８のいずれかに記載の錠剤の製造方法。

１０．賦形剤中に、有効成分を含有する顆粒を含み、

錠剤本体の表面にのみ滑沢剤を有し、且つ、

前記顆粒が、高圧で打錠すると変性又は失活する化合物の粉粒体材料である、錠剤。

１１．賦形剤中に、有効成分を含有する顆粒を含み、

錠剤本体の表面にのみ滑沢剤を有し、且つ、

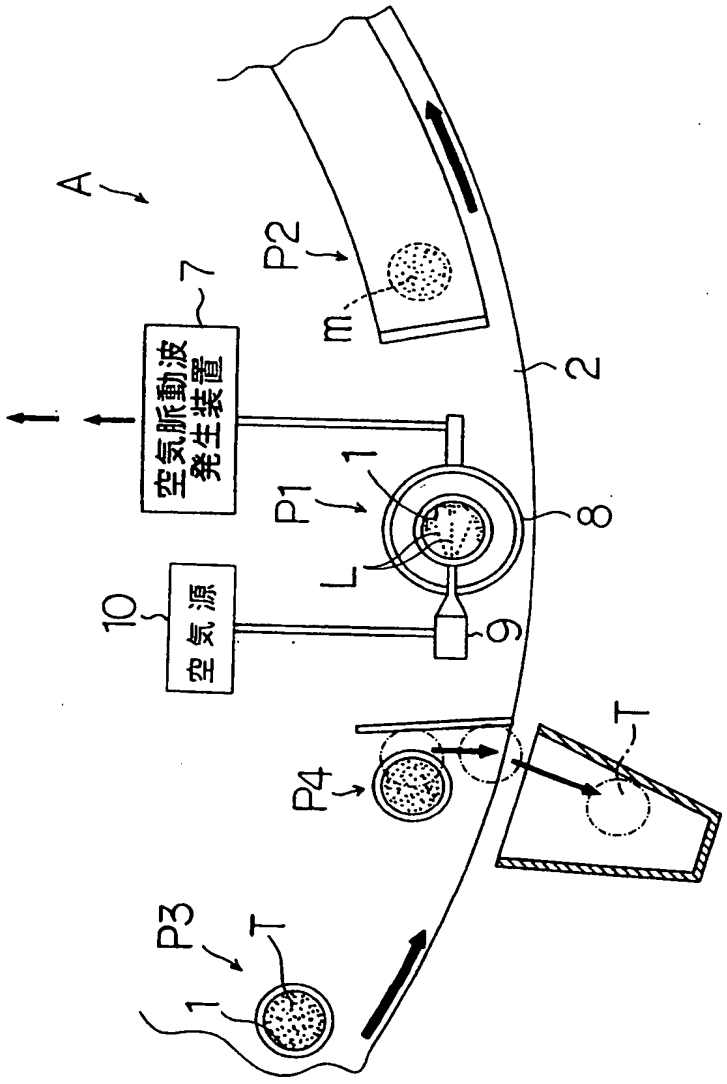
前記顆粒が、固体分散体粉粒体である、錠剤。

１２．前記滑沢剤の使用量が、一錠剤当り、０．０００１重量％以上０．２重量％以下とされている、請求項１０又は請求項１１に記載の錠剤。

１３．錠剤本体の形状が、異形であることを特徴とする、請求項１０～１２のいずれかに記載の錠剤。

１４．錠剤本体の表面に割線を有する、請求項１０～１３のいずれかに記載の錠剤。

第 1 図



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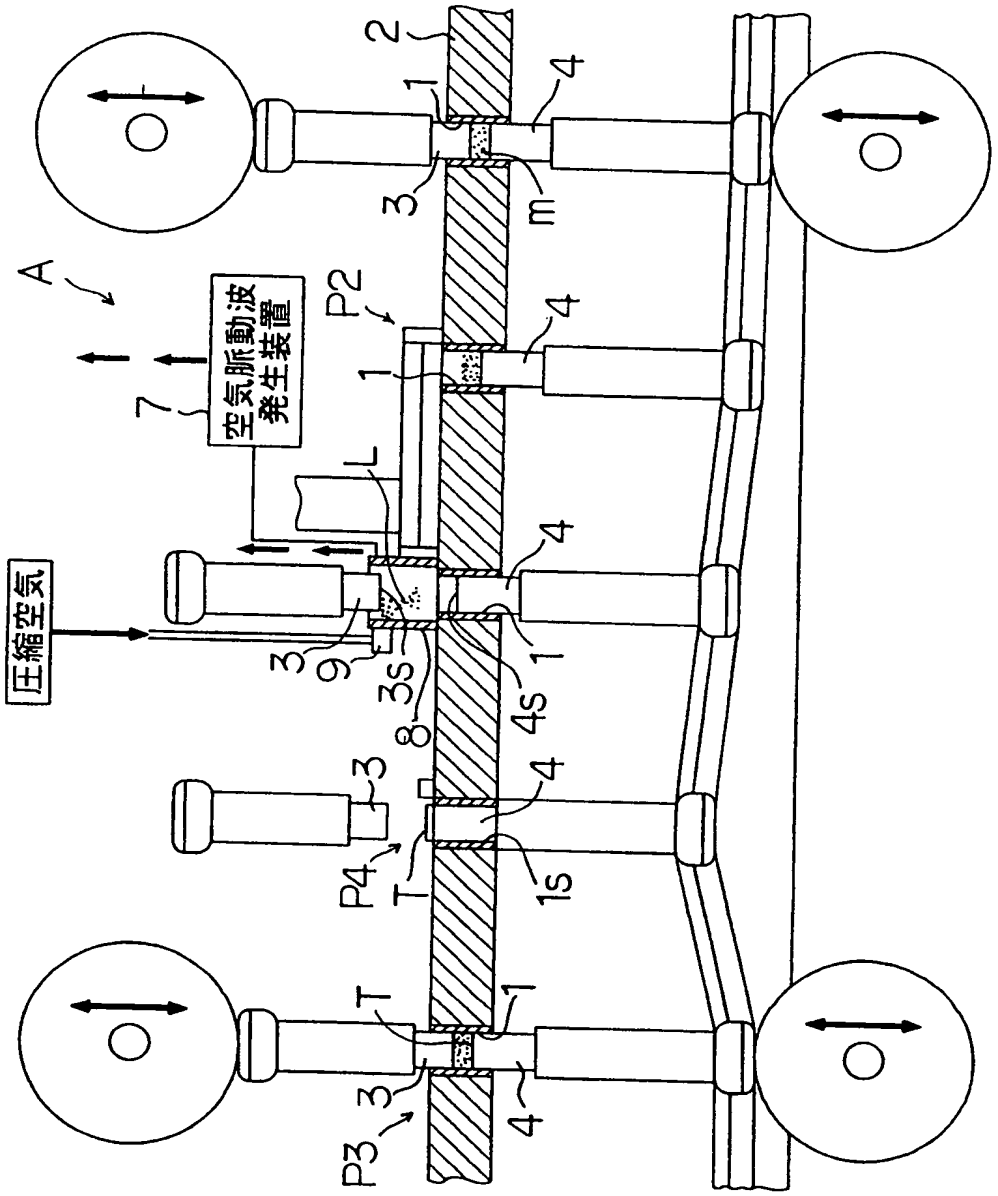
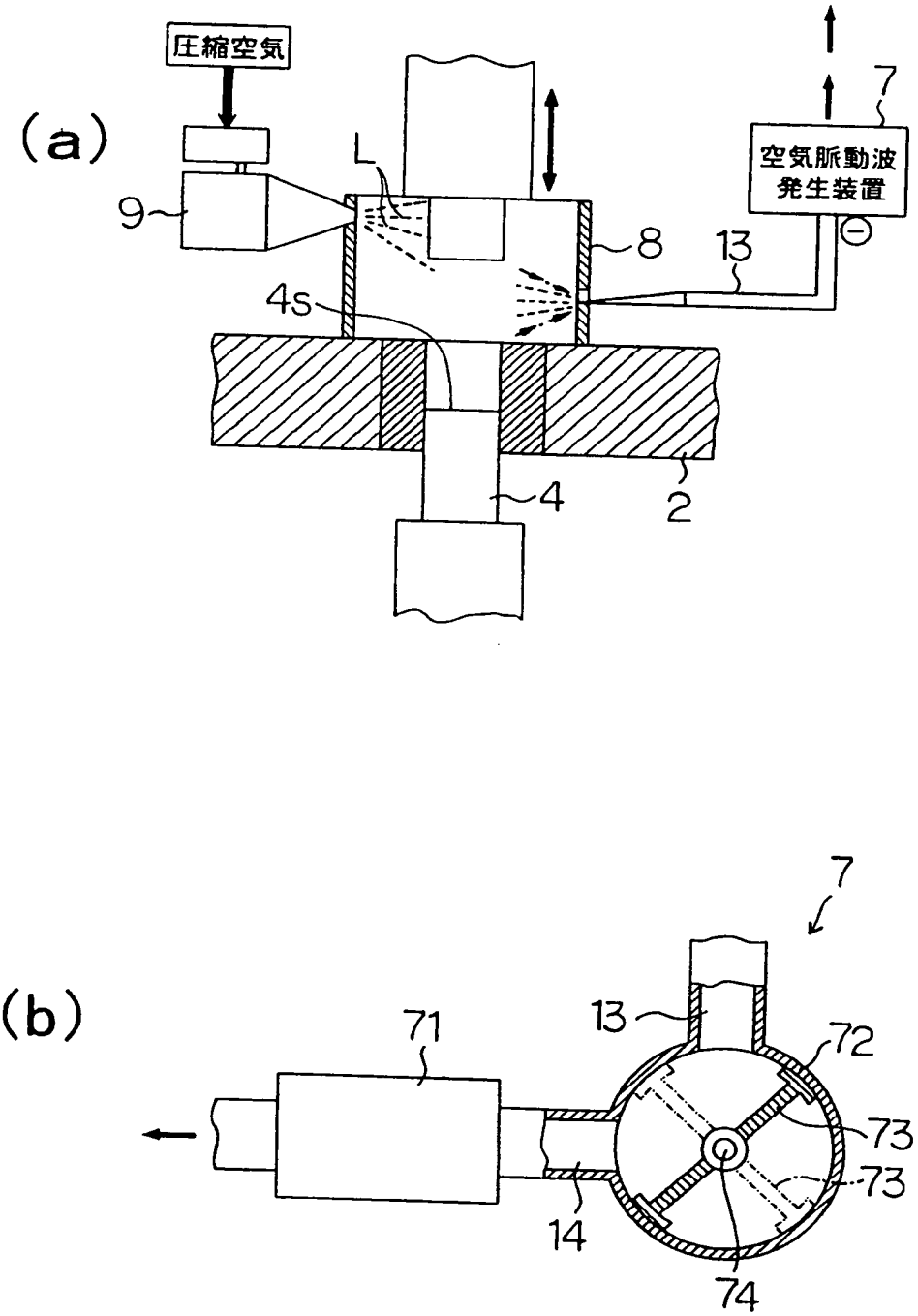
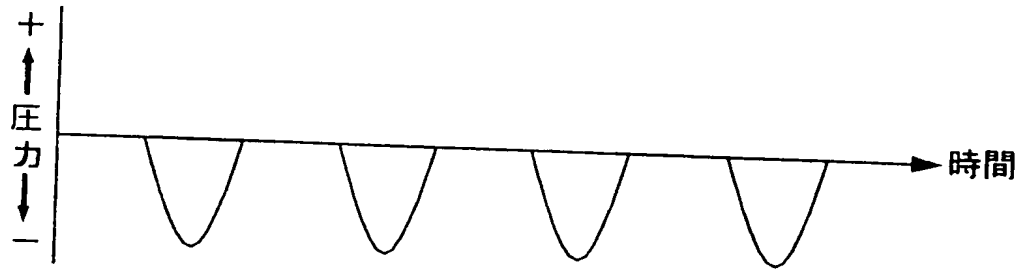


第 3 図

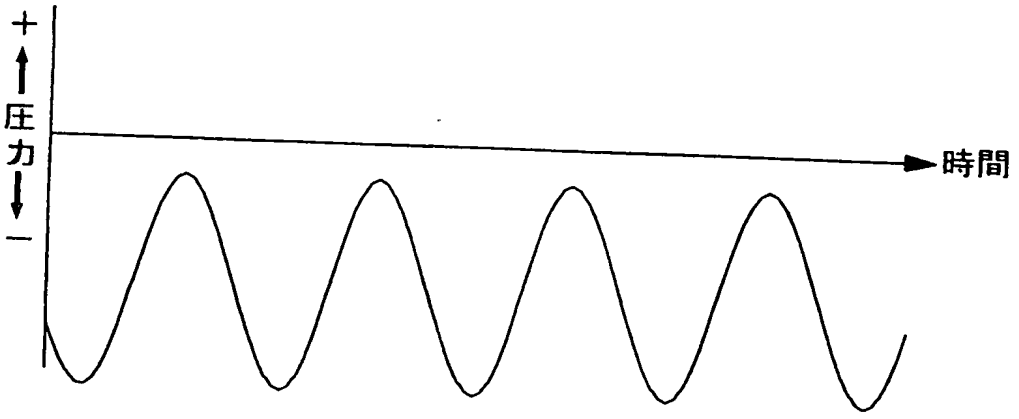


第 4 図

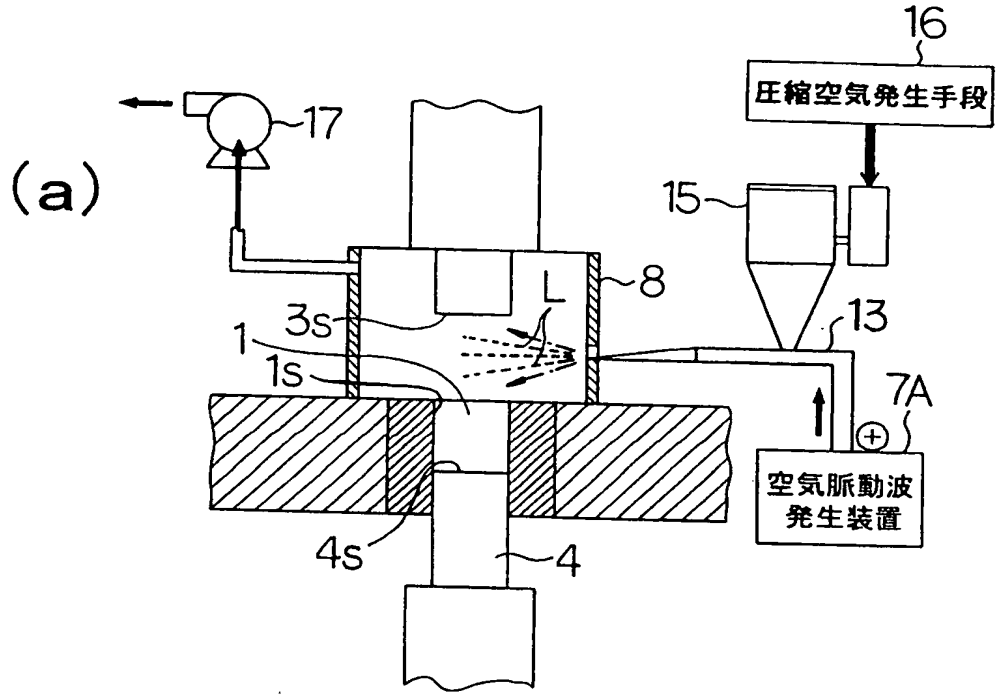
(a)



(b)



第 5 図


(a)
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圧縮空気発生手段
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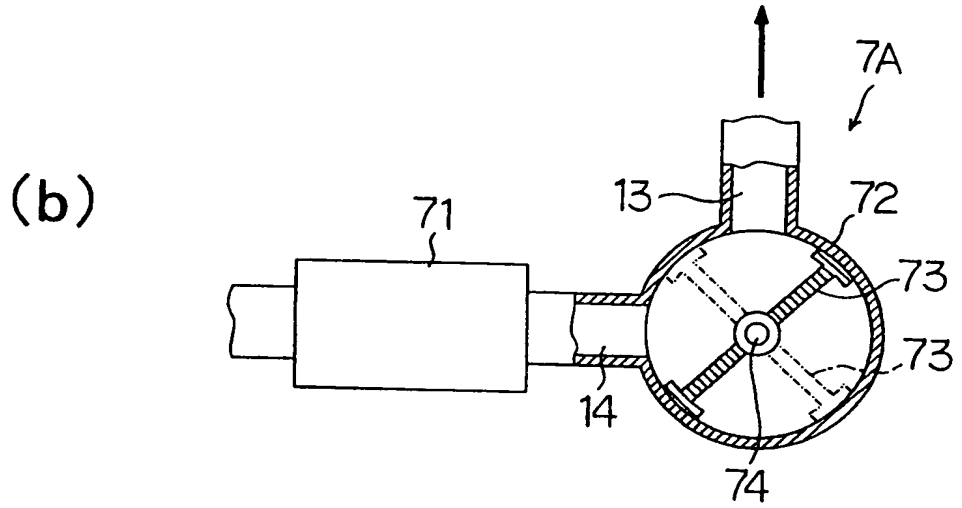
1s
13
7A
空気脈動波
発生装置
4s
4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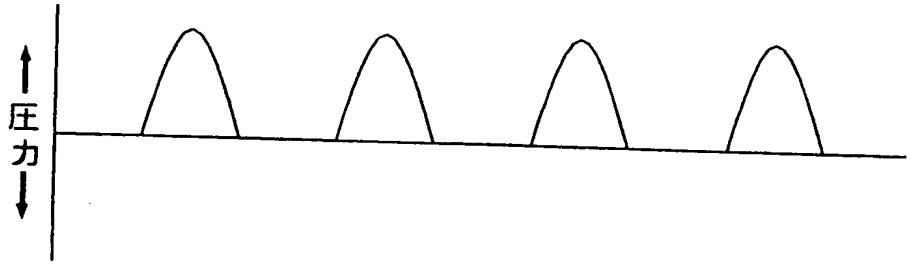
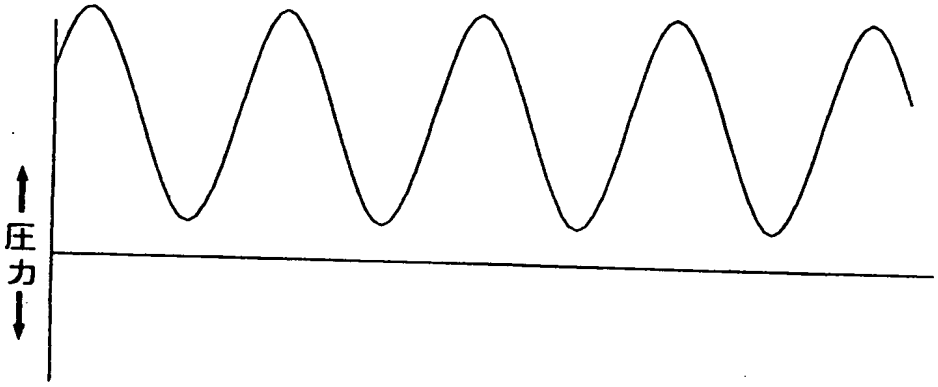
第 6 図

(a)



(b)



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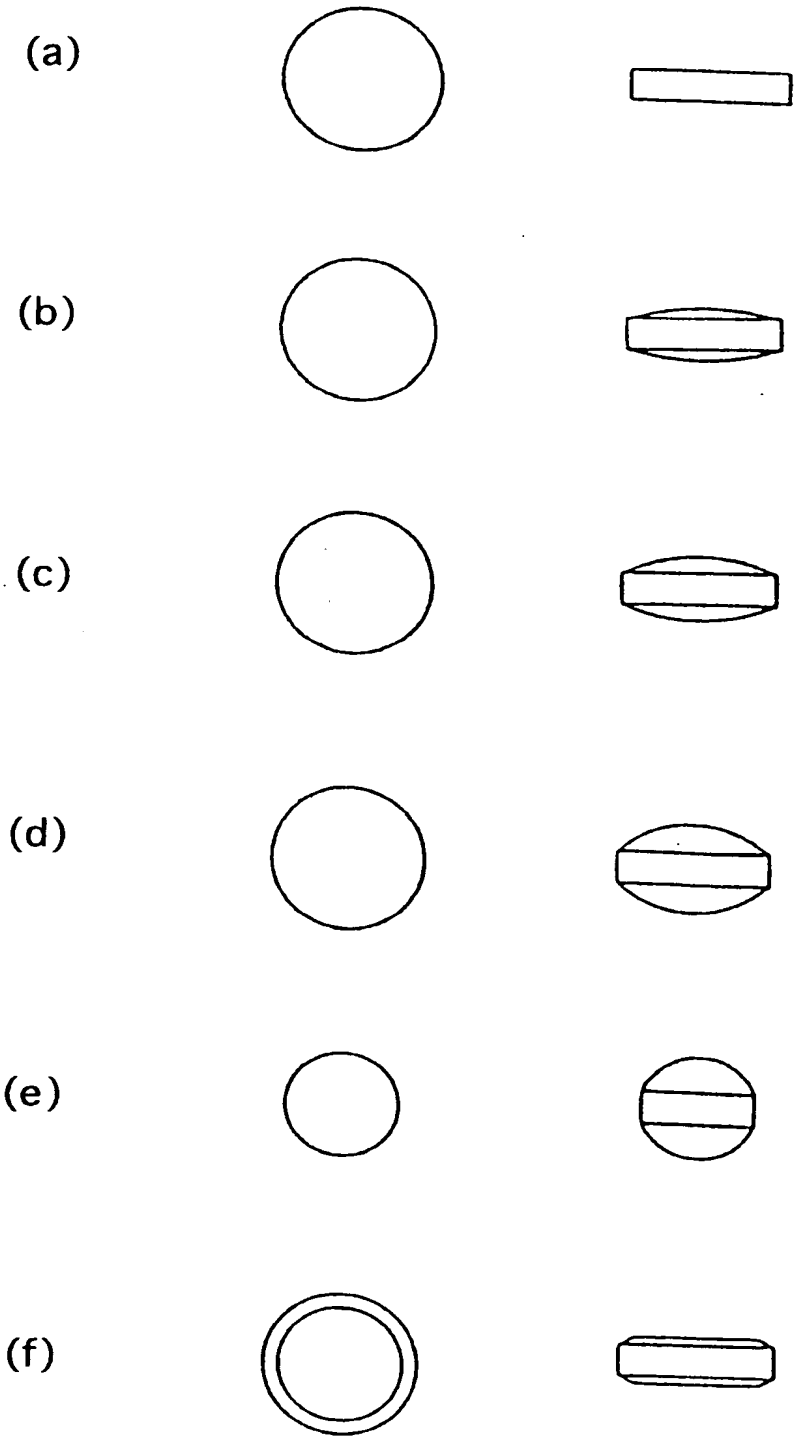


第 8 図

(a)

(b)

(c)

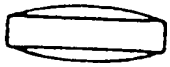
(d)

(e)

(f)

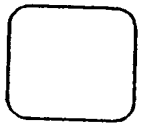
第 9 図

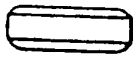
(a)



(b)

(c)





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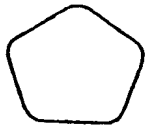

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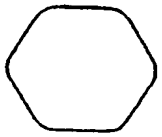
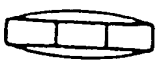




第10図

(a)

(b)

(c)

(d)

(e)

(f)

第 11 図

(a)

(b)

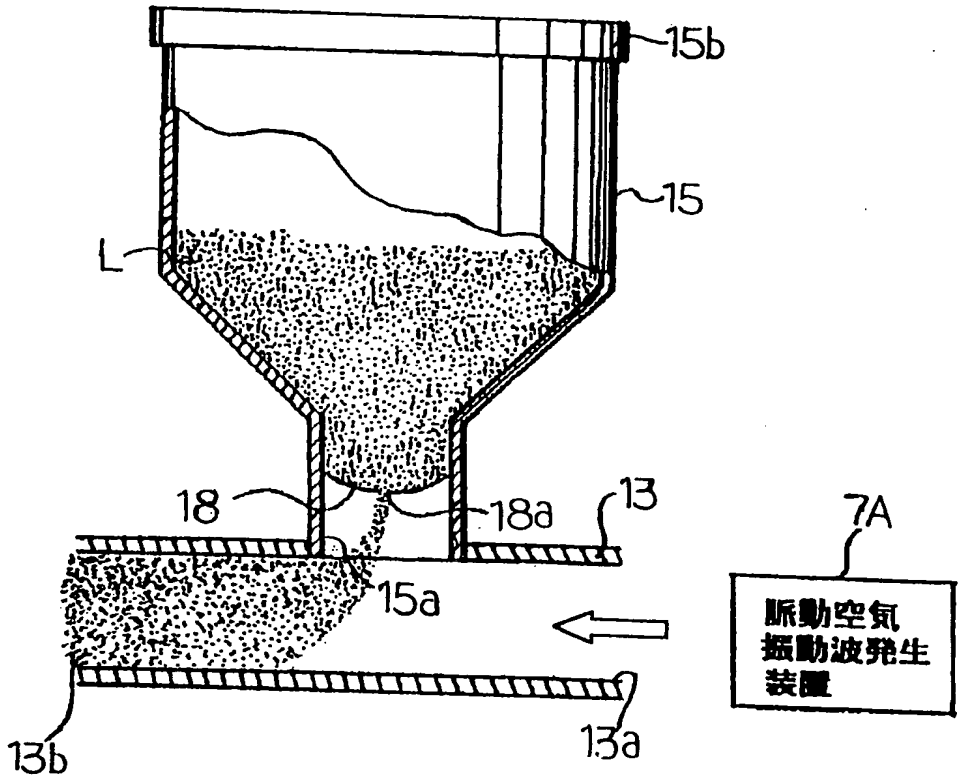
(c)

(d)

(e)

(f)

第12図



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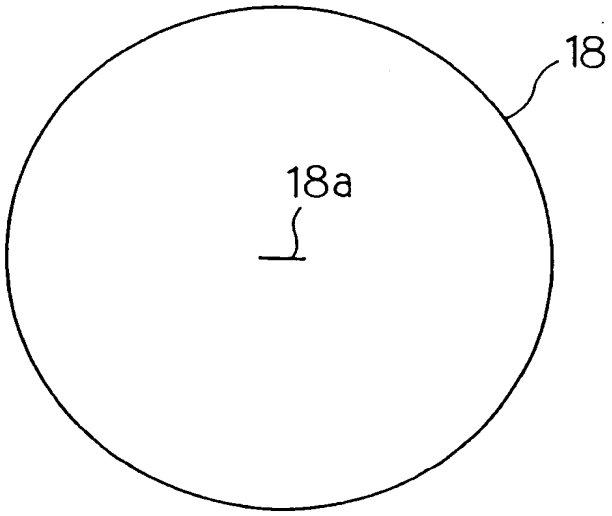
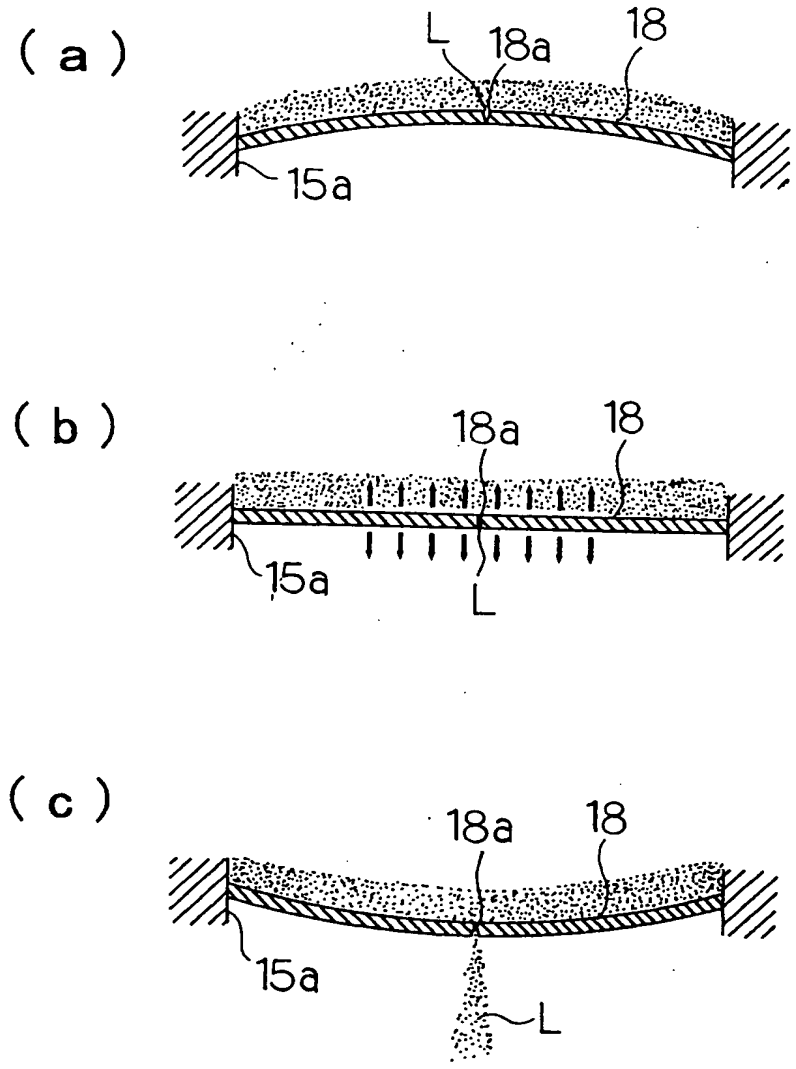
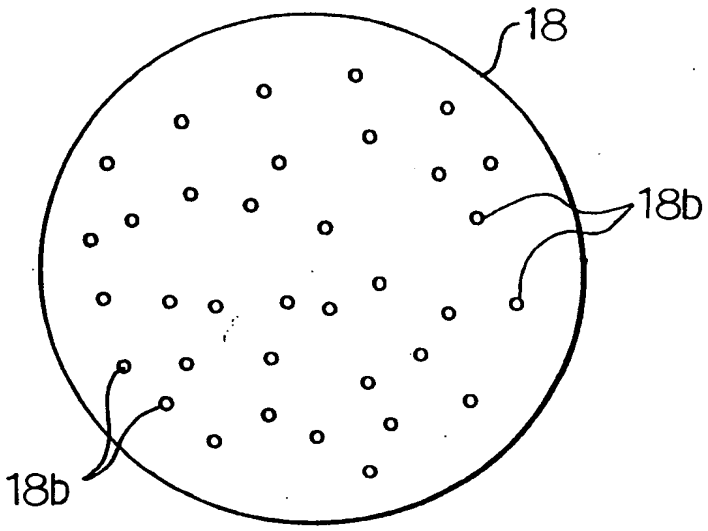
第13図



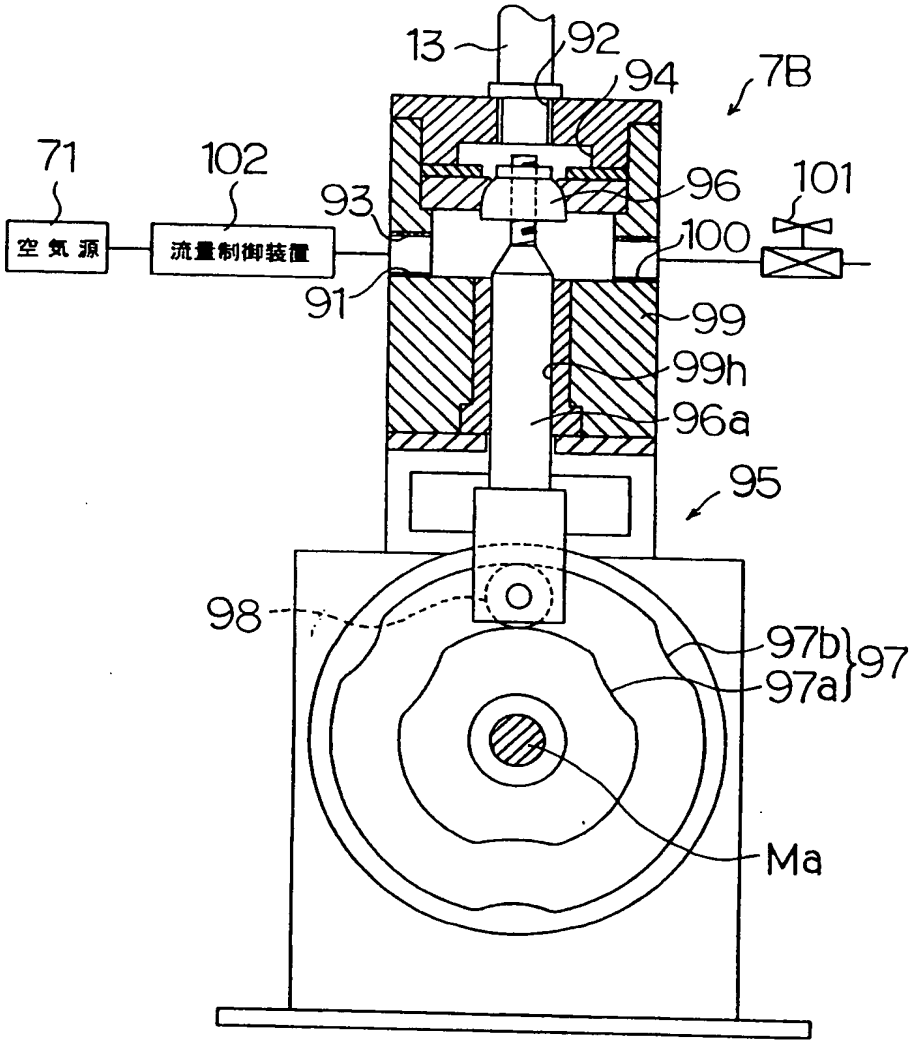
第14図



第15図



第 16 図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空気源
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97a
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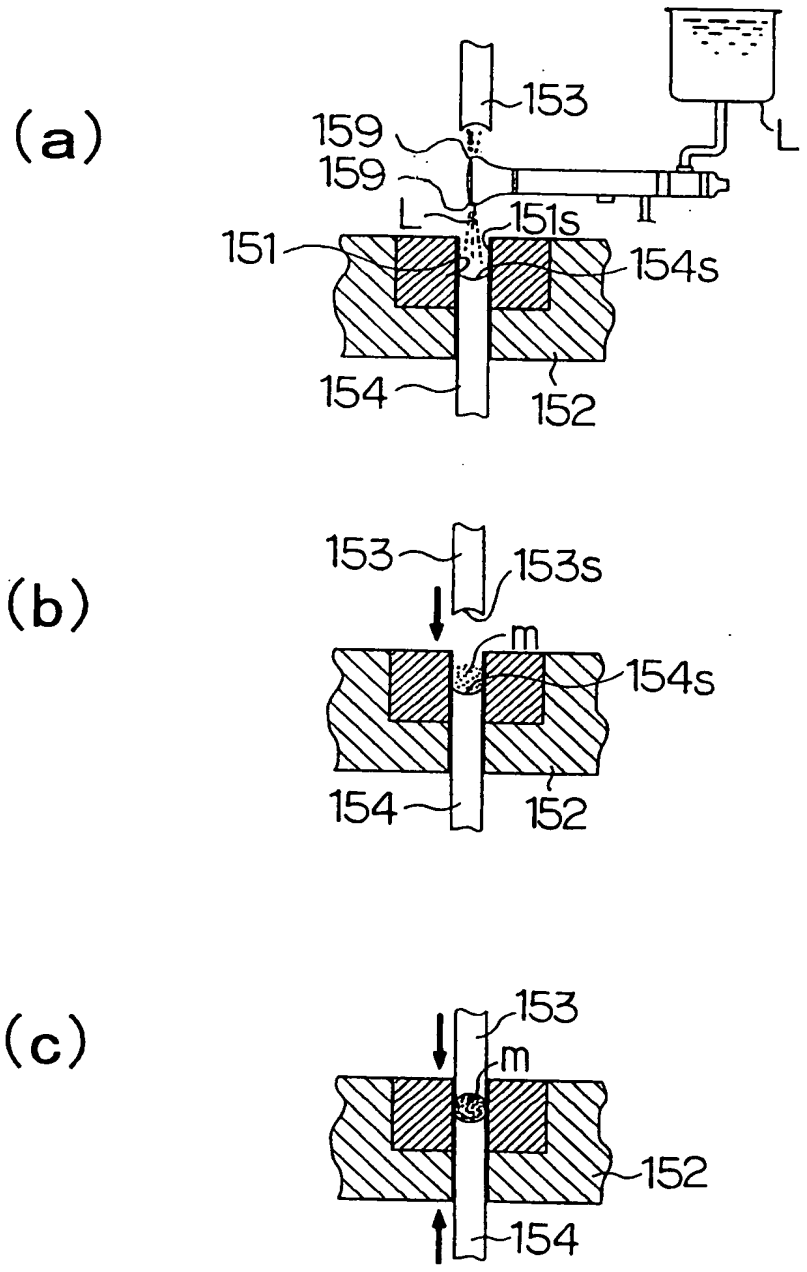
第17図


(a)
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(c)
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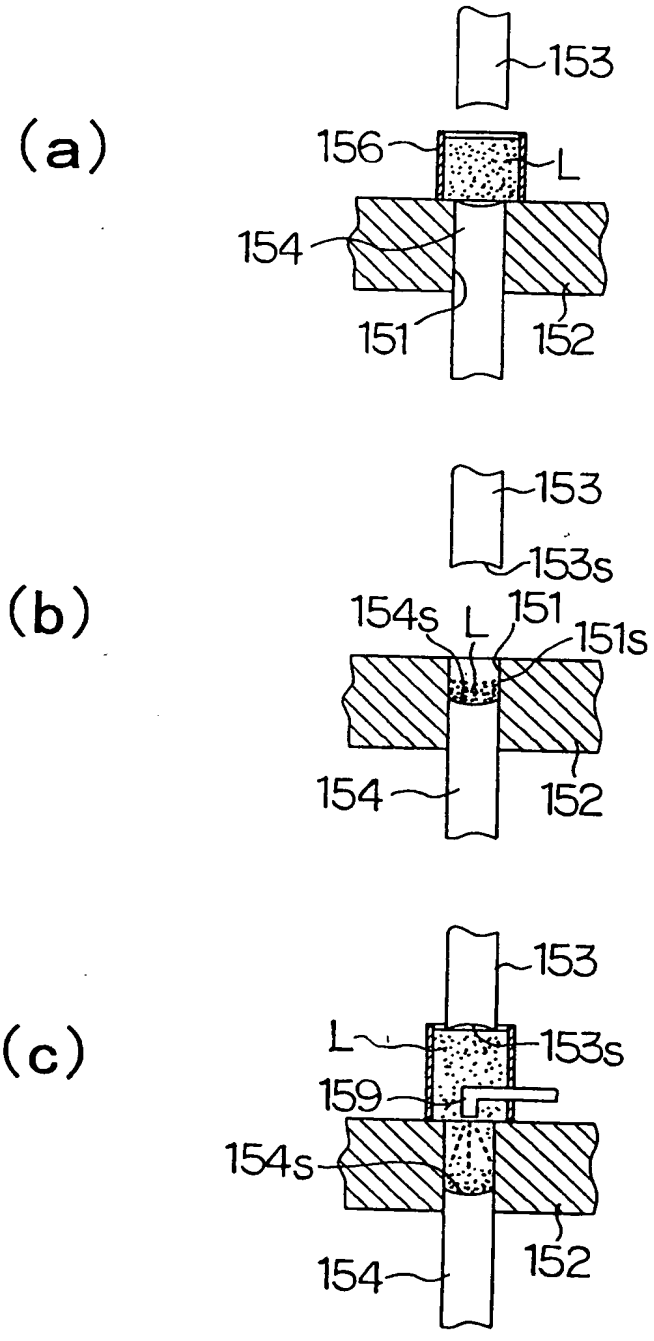
m
152
154

第 18 図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(c)
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152

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/01861

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] A61J3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] A61J3/10, B30B11/00, 11/08, A61K9/00-9/72, 47/00-47/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Toroku Jitsuyo Shinan Koho 1994-1999
Kokai Jitsuyo Shinan Koho 1971-1999 Jitsuyo Shinan Toroku Koho 1996-1999

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 45-22959, B1 (Carter Wallace Inc.), 3 August, 1970 (03. 08. 70), Column 1, line 26 to column 2, line 6 (Family: none)	1, 3, 5-10 12-14
Y	JP, 7-124231, A (Kyowa Hakko Kogyo Co., Ltd.), 16 May, 1995 (16. 05. 95), Full text ; all drawings & EP, 650826, A1 & US, 5700492, A	1-14
Y	JP, 2-206, A (Fujisawa Pharmaceutical Co., Ltd.), 5 January, 1990 (05. 01. 90), Full text & EP, 315964, A & US, 5093372, A	2, 4-9, 11-14
Y	JP, 62-187598, A (University of Bath), 15 August, 1987 (15. 08. 87), Full text ; all drawings & GB, 2183538, A & EP, 225803, A & US, 4832880, A	1-14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 July, 1999 (08. 07. 99)	21 July, 1999 (21. 07. 99)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/01861

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 8-277218, A (Kyowa Hakko Kogyo Co., Ltd.), 22 October, 1996 (22. 10. 96), Claims 1, 3 ; Figs. 1, 2 (Family: none)	6, 13, 14

国際調査報告

国際出願番号 PCT／JP99／01861

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cl⁶ A61J 3／10

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl⁶ A61J 3/10, B30B 11/00 11/08, A61K 9/00-9/72 47/00-47/48

最小限資料以外の資料で調査を行った分野に含まれるもの

日本国実用新案公報 1922－1996年
日本国公開実用新案公報 1971－1999年
日本国登録実用新案公報 1994－1999年
日本国実用新案登録公報 1996－1999年

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

C. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
Y	JP, 45-22959, B1 (カーター・ワレス・インコーポレーテッド) 3.8月.1970(03.08.70) 第1欄第26行－第2欄第6行 (ファミリーなし)	1, 3, 5-10 12-14
Y	JP, 7-124231, A (協和醗酵工業株式会社) 16.5月.1995(16.05.95) 全文, 全図 &EP, 650826, A1&US, 5700492, A	1－14
Y	JP, 2-206, A (藤沢薬品工業株式会社) 5.1月.1990(05.01.90) 全文 &EP, 315964, A&US, 5093372, A	2, 4-9, 11-14
Y	JP, 62-187598, A (ユニバーシティ オブ バス) 15.8月.1987(15.08.87) 全文, 全図 &GB, 2183538, A&EP, 225803, A&US, 4832880, A	1－14
Y	JP, 8-277218, A (協和醗酵工業株式会社) 22.10月.1996(22.10.96) 請求項1, 3, 図1, 2 (ファミリーなし)	6, 13, 14

☐ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

＊ 引用文献のカテゴリー

「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
08. 07. 99	21.07.99

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）		
日本国特許庁（ISA／JP） 郵便番号100－8915 東京都千代田区霞が関三丁目4番3号	大橋 賢一 印	3E	8825
	電話番号 03－3581－1101 内線 3345		

16 TT

特 許 協 力 条 約

PCT

国際予備審査報告

(法第１２条、法施行規則第56条)
〔ＰＣＴ３６条及びＰＣＴ規則70〕

出願人又は代理人の書類記号　１１１３２	今後の手続きについては、国際予備審査報告の送付通知（様式ＰＣＴ／ＩＰＥＡ／４１６）を参照すること。	
国際出願番号 ＰＣＴ／ＪＰ９９／０１８６１	国際出願日 (日.月.年)　０７．０４．９９	優先日 (日.月.年)　０８．０４．９８
国際特許分類（ＩＰＣ） Ｉｎｔ．Ｃｌ' Ａ６１Ｊ　３／１０		
出願人（氏名又は名称） 協和醗酵工業株式会社		

1．　国際予備審査機関が作成したこの国際予備審査報告を法施行規則第57条（ＰＣＴ３６条）の規定に従い送付する。

2．　この国際予備審査報告は、この表紙を含めて全部で　3　ページからなる。

☐ この国際予備審査報告には、附属書類、つまり補正されて、この報告の基礎とされた及び／又はこの国際予備審査機関に対してした訂正を含む明細書、請求の範囲及び／又は図面も添付されている。
（ＰＣＴ規則70.16及びＰＣＴ実施細則第６０７号参照）
この附属書類は、全部で＿＿＿＿＿＿ページである。

3．　この国際予備審査報告は、次の内容を含む。

I ☒ 国際予備審査報告の基礎

II ☐ 優先権

III ☐ 新規性、進歩性又は産業上の利用可能性についての国際予備審査報告の不作成

IV ☐ 発明の単一性の欠如

V ☒ ＰＣＴ３５条(2)に規定する新規性、進歩性又は産業上の利用可能性についての見解、それを裏付けるための文献及び説明

VI ☐ ある種の引用文献

VII ☐ 国際出願の不備

VIII ☐ 国際出願に対する意見

国際予備審査の請求書を受理した日 ０７．０４．９９	国際予備審査報告を作成した日 ２３．０２．００
名称及びあて先 日本国特許庁（ＩＰＥＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	特許庁審査官（権限のある職員）　３Ｅ　８８２５ 大橋　賢一 電話番号　０３－３５８１－１１０１　内線　３３４５

様式ＰＣＴ／ＩＰＥＡ／４０９（表紙）（１９９８年７月）

国際予備審査報告

国際出願番号　ＰＣＴ／ＪＰ９９／０１８６１

Ⅰ．　国際予備審査報告の基礎

1．　この国際予備審査報告は下記の出願書類に基づいて作成された。（法第６条（ＰＣＴ１４条）の規定に基づく命令に応答するために提出された差し替え用紙は、この報告書において「出願時」とし、本報告書には添付しない。ＰＣＴ規則70.16, 70.17）

☒ 出願時の国際出願書類

☐ 明細書　第 ＿＿＿＿＿＿ ページ、　出願時に提出されたもの
明細書　第 ＿＿＿＿＿＿ ページ、　国際予備審査の請求書と共に提出されたもの
明細書　第 ＿＿＿＿＿＿ ページ、　＿＿＿＿＿＿ 付の書簡と共に提出されたもの

☐ 請求の範囲　第 ＿＿＿＿＿＿ 項、　出願時に提出されたもの
請求の範囲　第 ＿＿＿＿＿＿ 項、　ＰＣＴ１９条の規定に基づき補正されたもの
請求の範囲　第 ＿＿＿＿＿＿ 項、　国際予備審査の請求書と共に提出されたもの
請求の範囲　第 ＿＿＿＿＿＿ 項、　＿＿＿＿＿＿ 付の書簡と共に提出されたもの

☐ 図面　第 ＿＿＿＿＿＿ ページ／図、　出願時に提出されたもの
図面　第 ＿＿＿＿＿＿ ページ／図、　国際予備審査の請求書と共に提出されたもの
図面　第 ＿＿＿＿＿＿ ページ／図、　＿＿＿＿＿＿ 付の書簡と共に提出されたもの

☐ 明細書の配列表の部分　第 ＿＿＿＿＿＿ ページ、　出願時に提出されたもの
明細書の配列表の部分　第 ＿＿＿＿＿＿ ページ、　国際予備審査の請求書と共に提出されたもの
明細書の配列表の部分　第 ＿＿＿＿＿＿ ページ、　＿＿＿＿＿＿ 付の書簡と共に提出されたもの

2．　上記の出願書類の言語は、下記に示す場合を除くほか、この国際出願の言語である。

上記の書類は、下記の言語である ＿＿＿＿＿＿ 語である。

☐ 国際調査のために提出されたＰＣＴ規則23.1(b)にいう翻訳文の言語
☐ ＰＣＴ規則48.3(b)にいう国際公開の言語
☐ 国際予備審査のために提出されたＰＣＴ規則55.2または55.3にいう翻訳文の言語

3．　この国際出願は、ヌクレオチド又はアミノ酸配列を含んでおり、次の配列表に基づき国際予備審査報告を行った。

☐ この国際出願に含まれる書面による配列表
☐ この国際出願と共に提出されたフレキシブルディスクによる配列表
☐ 出願後に、この国際予備審査（または調査）機関に提出された書面による配列表
☐ 出願後に、この国際予備審査（または調査）機関に提出されたフレキシブルディスクによる配列表
☐ 出願後に提出した書面による配列表が出願時における国際出願の開示の範囲を超える事項を含まない旨の陳述書の提出があった
☐ 書面による配列表に記載した配列とフレキシブルディスクによる配列表に記録した配列が同一である旨の陳述書の提出があった。

4．　補正により、下記の書類が削除された。
☐ 明細書　第 ＿＿＿＿＿＿ ページ
☐ 請求の範囲　第 ＿＿＿＿＿＿ 項
☐ 図面　図面の第 ＿＿＿＿＿＿ ページ／図

5．☐ この国際予備審査報告は、補充欄に示したように、補正が出願時における開示の範囲を越えてされたものと認められるので、その補正がされなかったものとして作成した。（ＰＣＴ規則70.2(c)　この補正を含む差し替え用紙は上記１．における判断の際に考慮しなければならず、本報告に添付する。）

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国際予備審査報告

国際出願番号 PCT／JP99／01861

V. 新規性、進歩性又は産業上の利用可能性についての法第１２条（ＰＣＴ３５条(2)）に定める見解、それを裏付ける文献及び説明

1. 見解

新規性（N）	請求の範囲	1－14	有
	請求の範囲		無
進歩性（ＩＳ）	請求の範囲		有
	請求の範囲	1－14	無
産業上の利用可能性（ＩＡ）	請求の範囲	1－14	有
	請求の範囲		無

2. 文献及び説明（ＰＣＴ規則70.7）

請求の範囲1,3,5-10,12-14に関し、国際調査引用文献１（JP,45-22959,B1（ｶｰﾀｰ・ﾜﾚｽ・ｲﾝｺｰﾎﾟﾚｰﾃｯﾄﾞ）3.8月.1970(03.08.70)第１欄第２６行－第２欄第６行（ファミリーなし））には、高圧で変性する活性物質を含む錠剤を低圧で打錠する際に、打錠機に錠剤粒子の一部が付着してしまうことが記載されている。そして、同引用文献２（JP,7-124231,A（協和醗酵工業株式会社）16.5月.1995(16.05.95)全文，全図&EP,650826,A1&US,5700492,A）に、打錠の際の材料付着を防止する空気脈動波を利用した外部滑沢式打錠機が記載されている。
従って、高圧で変性する活性物質を含む錠剤を、前記引用文献２記載の打錠機を用いて製造することは、当業者にとって容易な製法上の選択である。

次に、請求の範囲2,4-9,11-14に関し、同引用文献３（JP,2-206,A（藤沢薬品工業株式会社）5.1月.1990(05.01.90)全文&EP,315964,A&US,5093372,A）には、難溶性の化合物を固体分散体へ導いて、造粒や打錠し、生体吸収性を高めることが記載されている。そして、同引用文献４（JP,62-187598,A（ﾕﾆﾊﾞｰｼﾃｨ ｵﾌﾞ ﾊﾞｽ）15.8月.1987(15.08.87)全文，全図&GB,2183538,A&EP,225803,A&US,4832880,A）に、低溶解性医薬の場合に外部滑沢式打錠方法が適することが記載されている。
従って、固体分散体粉粒体を用いた錠剤を、前記引用文献２記載の打錠機を用いて製造することは、当業者にとって容易な製法上の選択である。

なお、請求の範囲6,13,14に関し、同引用文献５（JP,8-277218,A（協和醗酵工業株式会社）22.10月.1996(22.10.96)請求項１，３，図１，２（ファミリーなし））に、杵に凸部を設けて、打錠後の錠剤に割り溝を付けることが記載されているように、杵や臼の形状を変更し錠剤の形状を変更することは慣用手段である。

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Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 11132	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP99/01861	International filing date (*day/month/year*) 07 April 1999 (07.04.99)	Priority date (*day/month/year*) 08 April 1998 (08.04.98)
International Patent Classification (IPC) or national classification and IPC A61J 3/10		
Applicant KYOWA HAKKO KOGYO CO., LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 April 1999 (07.04.99)	23 February 2000 (23.02.2000)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP99/01861

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:

pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP99/01861

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-14	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-14	NO
Industrial applicability (IA)	Claims	1-14	YES
	Claims		NO

2. Citations and explanations

Regarding the subject matter of claims 1, 3, 5-10, and 12-14, document 1 [JP, 45-22959, B1 (CARTER WALLACE, INC.), 3 August 1970 (03.08.70), column 1, line 26 to column 2, line 6 (Family: none)] cited in the ISR discloses causing some of the tablet granules to adhere to a tablet stamping machine when stamping at low pressure a tablet that includes an active substance that denatures at high pressure. Also, document 2 [JP, 7-124231, A (KYOWA HAKKO KOGYO CO., LTD.), 16 May 1995 (16.05.95), entire text, all drawings & EP, 650826, Al & US, 5700492, A] cited in the ISR discloses an external lubrication-type tablet stamping machine that utilizes a pulsating air wave to prevent material adhesion when stamping tablets.

Therefore manufacturing a tablet that includes an active substance that denatures at high pressure using the tablet stamping machine disclosed in the aforesaid document 2 is merely the selection of an easy manufacturing method for a person skilled in the art.

Next, regarding the subject matter of claims 2, 4-9, and 11-14, document 3 [JP, 2-206, A (FUJISAWA YAKUHIN KOGYO K.K.), 5 January 1990 (05.01.90), entire text & EP, 315964, A & US, 5093372, A] cited in the ISR discloses making an insoluble compound into a solid dispersion, and making granules or stamping tablets, and thereby increasing biological absorption. Also, document 4 [JP, 62-187598, A (UNIVERSITY OF BATH), 15 August 1987 (15.08.87), entire text, all drawings & GB, 2183538, A & EP, 225803, A & US, 4832880, A] cited in the ISR discloses using an external lubrication-type table stamping method for chemicals with low solubility.

Therefore manufacturing a tablet that uses solid dispersion granules using the tablet stamping machine disclosed in the aforesaid document 2 is merely the selection of an easy manufacturing method for a person skilled in the art.

Furthermore, regarding the subject matter of claims 6, 13, and 14, document 5 [JP, 8-277218, A (KYOWA HAKKO KOGYO CO., LTD.), 22 October 1996 (22.10.96), claims 1, 3; Figs. 1, 2 (Family: none)] cited in the ISR discloses providing a projecting part in the pestle and adding splitting grooves in the tablet after tablet stamping, so modifying the shape of the pestle or mortar and modifying the shape of the tablet is a commonly used means.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 070 496 A1

(12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

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(51) Int. Cl.[7]: **A61J 3/10**

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AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **08.04.1998 JP 9644198**

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(54) TABLET MANUFACTURING METHOD AND TABLET

(57) According to the tablet production method of the present invention, tablet is produced by compressing molding material by means of punches and dies comprising the steps of using powdered or granular material including compound which is denaturalized or inactivated when tabletted at high pressure is used as the molding material, housing the punches and the dies in a spraying chamber, generating pulsating vibration air and spraying lubricant mixed in air in the spraying chamber, applying the lubricant on the surfaces of the punches and the dies while the lubricant sprayed in the spraying chamber is mixed with the pulsating vibration air, and tabletting the molding material by means of the punches applied with the lubricant on the surface thereof and the dies applied with the lubricant on the surface thereof.

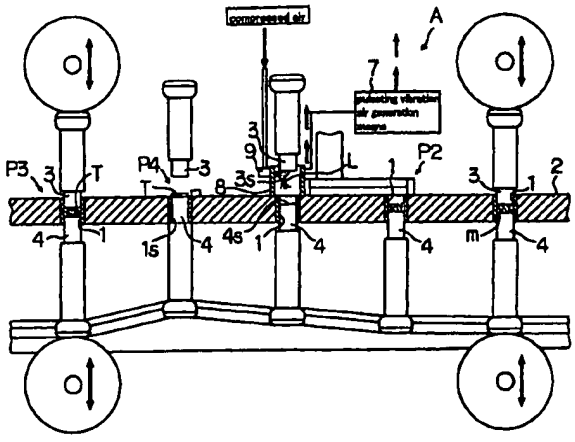

Fig. 2

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Description

Technical Field

[0001] The present invention relates to a tablet production method, particularly to a tablet production method wherein a tablet including compound powdered or granulated which is apt to be denaturalized or inactivated when tabletted at high pressure can be manufactured without denaturallzing or deactivating drugs and also to a tablet production method wherein a tablet including solid dispersion powdered or granulated can be manufactured while keeping the function of the solid dispersion powdered or granulated.

[0002] The present invention also relates to a tablet including compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure without denaturalized or inactivated and also to a tablet including solid dispersion powdered or granulated keeping the function thereof.

Background Art

[0003] A tablet has an advantage of easy dosing and is the most preferable type for patient as oral administration and intrabuccal administration.

[0004] Such a tablet is generally produced by an internal lubricant method and an external lubricant spraying method.

[0005] According to the internal lubricant method, in order to prevent that molding material to be tabletted is apt to attach on punches and dies and gride between the punches and dies is apt to be caused so as to execute smooth tabletting and also prevent defective goods with sticking, capping or laminating, magnesium stearate, lauryl sodium sulphate, talc and so on are mixed in the molding material to be tabletted other than active compound and diluting agent and the mixture is compressed to obtain a tablet.

[0006] As an external lubricant spraying method, a tablet production method has been disclosed in, for example, JP-B-41-11273 and JP-A-56-14098.

[0007] Fig.17 schematically shows procedures of the tablet production method disclosed in JP-B-41-11273.

[0008] According to the method comprised of charging a fixed amount of material to be tabletted in a die, tabletting the charged material in the die by means of a pair of an upper and a lower punches, and discharging the tablet, as a procedure before molding material is charged in the die 151 as shown in Fig.17(a), a spray nozzle 159 for spraying lubricant L is provided above the die 151 and lubricant L is applied on a lower surface 153s of the upper punch 153 and an upper surface 154s of the lower punch 154, both of which are provided for the die 151 which comes to a place where the spray nozzle 159 is placed. Then molding material is charged in the die 151 as shown in Fig. 17(b), and the charged material m is compressed by means of the upper punch 153 on which lower surface 153s is applied with lubricant L and the lower punch 154 of which upper surface 154s is applied with lubricant as shown in Fig.17(c).

[0009] The member indicated by the numeral 152 in Fig.17 shows a rotary table provided with the die 151 (The same numeral is used in Fig.18.).

[0010] Fig.18 shows a tablet production method described in JP-A-56-14098.

[0011] According to this method, before molding material is charged in a die 151, a spray 156 for spraying lubricant L and a nozzle 159 for spraying air are provided above the die 151. Lubricant L is sprayed in the spray 156 when the die 151 comes where the spray 156 is provided as shown in Fig.18(a), lubricant is applied on an upper surface 154s of a lower punch 154 provided for the die 151 as shown in Fig.18(b). As shown in Fig.18(c), compressed air is sprayed on the lower punch 154 at a position where the nozzle 159 is provided, lubricant L applied on the upper surface 154s of the lower punch 154 is blown upwardly to be dispersed, then the dispersed lubricant L is attached on an inner wall 151s of the die 151 and a lower surface 153s of an upper punch 153. Thereafter, molding material m is compressed to produce a tablet by means of lubricated inner wall 151s of the die 151, lubricated lower surface 153s of the upper punch 153, and lubricated upper surface 154s of the lower punch 154.

[0012] However, some drugs are destabilized or dissolved or its elution becomes slow because its crystal is deformed by the pressure applied at the time of tabletting (usually 1 ton/c m^2 - 2 ton/cm^2), friction, and heating. (Hereinafter such substances are called "drugs which is denaturalized or inactivated when tabletted at high pressure" in this specification.)

[0013] As a method for tabletting such drugs, an internal lubricant method wherein lubricant such as macrogol 6000, sucrose esters of fatty acid, and so on are added to molding material has been already suggested. (Refer to the summary of 11^{th} pharmaceuticals and powder design symposium, 79 (1994) and JP-A-8-175996.)

[0014] Solid dispersing pharmaceuticals wherein compound is dispersed in low molecular carrier or high molecular carrier has been recently developed.

[0015] Such solid dispersing pharmaceuticals are highly effective to heighten solubility of drugs which is slight soluble and has low absorbability into the body in case of oral dosage, to control releasing speed of drugs, and to improve

bioavailability of drugs.

[0016] Solid dispersion pharmaceuticals are generally produced by a fusion method wherein drugs and carrier are heated and fused and thereafter cooled down. Or they are produced by means of a solvent method wherein drugs and carrier are dissolved in an appropriate solvent and the solvent is removed. Or they are produced by a fusion-solvent method wherein a fusion method and a solvent method are combined.

[0017] However, an internal lubricant means wherein a tablet including compound which are denaturalized or inactivated when tabletted at high pressure is produced by adding lubricant such as macrogol 6000, sucrose esters of fatty acid, and so on in molding material isn't an adequate method. According to drugs, compressed tablet may be destabilized or decomposed, or elution may become slow even if lubricant such as macrogol 6000, sucrose esters of fatty acid, and so on is added to molding material.

[0018] Further, depending on drugs, they may attach on punches and dies at the time of tabletting. As the result, produced tablet may cause sticking, capping and laminating.

[0019] When solid dispersion is produced into a tablet as solid dispersing pharmaceuticals wherein solid dispersion is pulverized into a suitable particle size and the pulverized substance and lubricant are mixed according to the prior internal lubricant method, property of the solid dispersion tablet may be changed because of water repellency of lubricant included in the tablet. When lubricant is included in the tablet, high pressure is required to give practical hardness. However, the solid dispersion may be denaturalized because of high tabletting pressure and originally designed property (for example disintegrating time) isn't achieved.

[0020] Therefore, pharmaceuticals including drugs which are denaturalized or inactivated when tabletted at high pressure and solid dispersing pharmaceuticals are generally supplied as capsule in the market so far.

[0021] However, capsule is hard to be taken for elderly person and children because it floats on the water when taking with water. It has been requested by physician and so on to develop a tablet which sinks in the water and is easy to be swallowed when taking with water as pharmaceuticals including drugs which are denaturalized or inactivated when tabletted at high pressure and as solid dispersing pharmaceuticals.

[0022] Also capsule needs a body and a cap and its production takes a lot of labor as follows. Drugs which are denaturalized or inactivated when tabletted at high pressure and solid dispersion (powder and granule) are pulverized and charged in the body of capsule and the cap is covered thereon to be sealed.

[0023] Further, physician requests not only that pharmaceuticals conventionally supplied as capsule in the market is produced as a tablet but also that such tablet is dividable so that patient can take appropriate dosage.

[0024] The present invention has been developed in order to solve the above-mentioned problems. The object of the present invention is to provide a production method of tablet wherein a tablet including compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure can be easily produced without denaturalizing or deactivating such compound.

[0025] Another objet of the invention is to provide a tablet including solid dispersion powdered or granulated keeping function of the solid dispersing material, a tablet including compound which is denaturalized or inactivated when tabletted at high pressure without denaturalizing or deactivating such compound, and a dividable type tablet of these tablets which can keep its function when divided.

Disclosure of the Invention

[0026] The tablet production method in claim 1 is a tabletting method for compressing molding material by means of punches and dies. Powdered or granular material including compound which is denaturalized or inactivated when tabletted at high pressure is used as the molding material. The punches and the dies are housed in a spraying chamber. Pulsating vibration air is generated, and lubricant mixed in air is sprayed in the spraying chamber. The surfaces of punches and dies are applied with lubricant while lubricant sprayed in the spraying chamber is mixed with pulsating vibration air. Then molding material is tabletted by means of the punches and dies applied with the lubricant on the surface thereon.

[0027] Here in this specification "high pressure" means a required tabletting pressure for compressing molding material by an internal lubricant method and for producing a tablet having practical hardness. More specifically it means greater than or equal to 1 ton/cm^2.

[0028] "Compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure" means powdered and granule of compound which is apt to be denaturalized or inactivated when tabletted by means of an internal lubricant method. Specifically the examples of such compound are pharmaceuticals shown in the following tables 3 - 6, explained hereinafter.

[0029] "Powdered or granular material including compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure" may include diluting agent, binder, supplement such as solution adjuvant, solubilizer and disintegrant, corrigent, colorant, adjuvant for pharmaceuticals, antioxidant, preservative, opacifying agent, charge protector, aroma, sweetening agent, fluidizing agent, flavoring agent, and so on, if required, other than com-

pound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure. However, it doesn't include lubricant.

[0030] According to this production method, lubricant is sprayed in the spraying chamber wherein pulsating vibration air is generated and lubricant mixed with pulsating vibration air is applied on the surfaces of punches and dies. Comparing with prior external lubricant spraying method, lubricant can be uniformly applied on the surfaces of the punches and dies.

[0031] As a result, under the process wherein compound which is denaturalized or inactivated when tabletted at high pressure is tabletted, the compound is hard to be attached on the surfaces of the punches and dies so that such tablet as biochemical pharmaceuticals is produced without sticking, capping and laminating.

[0032] Moreover, lubricant is merely attached on the surface of tablet and isn't included inside of tablet. Therefore, comparing with a tablet including lubricant, produced tablet has practical hardness even if compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure is tabletted at low pressure (concretely under 1 ton/c m^2).

[0033] Several kinds of lubricant can be used for tablet production method of the present invention. Lubricant isn't specifically limited, for example, there are stearate acid metal salt (magnesium stearate, calcium stearate and so on), stearic acid, sodium lauryl sulfate, sodium lauryl magnesium, powdered gum arabic, carnauba wax, anhydrous silicic acid, magnesium oxide, silic acid hydrate, boric acid, fatty acid sodium salt, leucine, and so on which have been commonly used. One of them may be used solely or more than two of them may be combined.

[0034] As for diluting agent, there are several kinds, such as saccharides (lactose, sucrose, glucose, mannitol, and so on), starch (for example, potato, wheat, corn and so on), inorganic substance (calcium carbonate, calcium sulfate, sodium bicarbonate, sodium chloride, and so on), crystalline cellulose, powdered plant (powdered glycyrrhiza, powdered gentian, and so on).

[0035] Moreover, any kind of pulsating vibration air with different cycle and strength, regardless of positive pressure or negative pressure, may be used if air pressure of pulsating vibration air can achieve function of forcibly diffusing lubricant particle sprayed in the sampling chamber by generating air vibration all over the sampling chamber.

[0036] Conditions such as frequency and pressure of pulsating vibration air depend on size and shape of punches and dies of a tabletting machine, size and shape of a spraying chamber, how a lubricant spraying means is provided, and description of active compound. Therefore, conditions can't be simply defined and is defined based on experiments.

[0037] According to the tablet production method as set forth in claim 2, molding material is compressed by means of punches and dies. The method uses solid dispersion powdered or granulated as molding material. The punches and the dies are housed in a spraying chamber, pulsating vibration air is generated therein, and lubricant mixed in air is sprayed. The lubricant is applied on the surfaces of the punches and the dies while the lubricant sprayed in the spraying chamber is mixed with the pulsating vibration air and the molding material is tabletted by means of the lubricated punches and the lubricated dies.

[0038] "Solid dispersion powdered or granulated" in this specification means solid dispersion (powder or granule) ground into appropriate particle size.

[0039] More concretely explained, this tablet production method is effective for tabletting solid dispersion powdered or granulated including low molecule compounds of which elution is delayed and high molecule compounds which is apt to be dissolved and denaturalized when tabletted at high pressure according to an internal lubricant method.

[0040] As a carrier of solid dispersion, so called high molecule carrier can be used.

[0041] Generally there are pH dependent high molecular carrier, pH independent high molecular carrier, water-soluble high molecular carrier, and so on. Examples are as follows:

hydroxypropylmethylcellulose phthalate 220824 (HP50), hydroxypropylmethylcellulose phthalate 220731 (HP55), hydroxypropylmethylcellulose acetate succinate (A coat), carboxymethylethylcellulose (CMBC), cellulose acetate phthalate (CAP), metaacrylic acid copolymer LD (L30D55), meta acrylic acid copolymer S (S-100), aminoalkylmetaacylate copolymer E (soluble in stomach), polyvinyl acetal diethyl amino acetate (ABA), polyvinylpyrrolidone (K-25, 30, 90; PVP), ethyl cellulose (BC), metacrylic acid copolymer RS (RS30D), polyvinyl alcohol (PVA), metylcellulose (MC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose 2208 (METROSE 90SH), hydroxypropylmethylcellulose 2906 (METOLOSE 65SH), hydroxypropylmethylcellulose 2910 (METROLSE 60SH, TC-5R), sodium carboxymethylcellulose, dextrin, pullulane, gum arabic, tragacanth, propylene glocol alginate, agar powder, gelatin, starch, processed starch, phospholipid (lecithin), glucomannnan glucomannnan, and so on.

[0042] Such high molecular carrier may be used solely or some of them may be combined if required.

[0043] Particle size of high molecular carrier is usually less than or equal to 7000μm, more preferably less than or equal to 2000 μm. Conditions such as pressure, temperature, supplying speed, adding amount and supplying speed of water or plasticizer, and so on, according to the present invention, differ depending on the kind of used drugs, high

molecular carrier, dual-axis extruder, and so on. However, it is important to combine them so as to lower molding temperature under decomposition temperature of drugs and high molecular carrier. And it is also important to change them according to product characteristic expected to be produced.

[0044] The ratio (weight ratio) when drugs and high molecular carrier are mixed differs depending on kinds, object, membrane characteristic, and so on thereof. It is suitable at 0.1 - 999 of high molecular carrier for 1 drug, preferably 0.5 - 500, more preferably 1 - 50.

[0045] In a material including both compound which is unstable for heat and high molecular carrier, water solution or dispersant of plasticizer can be added to the material when or before the material is extruded with the dual-axis extruder. When this method is utilized, temperature of transition of high molecular carrier can be lowered. Therefore, molding temperature can be lower than the decomposition temperature of compound and high molecular carrier so that decomposition caused by the heat of drugs and high molecular carrier can be prevented. Of course, in a material which doesn't include both compound which is unstable for heat and high molecular carrier, water solution or dispersant of plasticizer can be added in a same manner.

[0046] As plasticizer for lowering the temperature of transition of high molecular carrier, compound which has been used as plasticizer for film coating in the field of manufacturing technique can be used. Such a compound is as follows;

cetanol, fatty acid polyoxyethylene-polyoxyp, macrogol (200, 300, 400, 600, 1000, 1500, 1540, 4000, 6000, 20000), triacetyne, triethyl citric (cytroflex), and so on.

[0047] Adding amount of plasticizer depends on used drugs and high molecular carrier, however its ratio is suitable at 1% - 80% for a molecular carrier, preferably at 5% - 50%.

[0048] Plasticizer may be directly added to the mixture of high molecular carrier and drugs at first or plasticizer dissolved or deipersed in the water may be added during molding. Adding method of platicizer isn't limited.

[0049] According to this tablet production method, lubricant is sprayed in the spraying chamber wherein pulsating vibration air is generated and the lubricant mixed with pulsating vibration air is applied on the surfaces of punches and dies. Therefore, lubricant can be applied uniformly on the surfaces of the punches and dies comparing with the prior external lubricant spraying means.

[0050] As the result, molding material hardly attaches on the surfaces of punches and dies in tabletting step of solid dispersion powdered or granulated so that produced tablet of solid dispersion doesn't cause sticking, capping and laminating.

[0051] Further, lubricant is attached only on the surface of produced tablet of solid dispersion and isn't included therein. Therefore, produced tablet of solid dispersion has practical hardness even if solid dispersion powdered or granulated is tabletted at low tabletting pressure comparing with a tablet of solid dispersion including lubricant therein.

[0052] According to this tablet production method, tablet of solid dispersion substance can be tabletted at low tabletting pressure so that property of solid dispersion substance isn't changed.

[0053] According to the tablet production method for compressing molding material by means of punches and dies as set forth in claim 3 powdered or granular material including compound which is denaturalized or inactivated when tabletted at high pressure is used as molding material. The punches and the dies are housed in a spraying chamber, the lubricant is applied on the surfaces of the punches and the dies while the lubricant sprayed in the spraying chamber is mixed with positive pulsating vibration air, and the molding material is tabletted by means of the punches applied with the lubricant on the surface thereof and the dies applied with the lubricant on the surface thereof.

[0054] According to this production method, lubricant mixed with positive pulsating vibration air is sprayed in the spraying chamber and is applied on the surfaces of the punches and dies. Lubricant can be uniformly applied on the surfaces of the punches and dies comparing with the prior external lubricant spraying method.

[0055] As a result, when tabletting compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure, such compound as denaturalized or inactivated when tabletted at high pressure hardly attaches on the surface of the punches and dies and produced biological pharmaceuticals doesn't cause sticking, capping, laminating, and so on.

[0056] Further, lubricant is attached only on the surfaces of tablet and isn't included therein. Produced tablet has practical hardness even if compound which is denaturalized or inactivated when tabletted at high pressure is tabletted at low tabletting pressure (concretely less than or equal to 1 ton/cm^2) comparing with the tablet including lubricant.

[0057] According to the tablet production method for compressing molding material by means of punches and dies as set forth in claim 4, solid dispersion powdered or granulated is used as the molding material. The punches and the dies are housed in a spraying chamber, lubricant is applied on the surfaces of the punches and the dies while the lubricant sprayed in the spraying chamber is mixed with positive pulsating vibration air, and the molding material is tabletted by means of the punches applied with the lubricant on the surface thereof and the dies applied with the lubricant on the surface thereof.

[0058] According to this method, lubricant mixed with positive pulsating vibration air is sprayed in the spraying

chamber and the mixed lubricant is applied on the surfaces of the punches and dies. Therefore, lubricant can be uniformly applied on the surfaces of the punches and dies comparing with the prior external lubricant spraying means.

[0059] As the result, molding material hardly attaches on the surfaces of the punches and dies when solid dispersion powdered or granulated is tabletted and produced tablet of solid dispersion doesn't cause sticking, capping, laminating and so on.

[0060] Further lubricant is attached only on the surface of produced tablet of solid dispersion and isn't included therein. Therefore, the produced tablet of solid dispersion has a hardness of practical level even if solid dispersion powdered or granulated is compressed at low tabletting pressure comparing with the tablet of solid dispersion including lubricant therein.

[0061] According to this tablet production method, solid dispersion can be tabletted at low tabletting pressure so that property of solid dispersion isn't changed.

[0062] According to the tablet production method as set forth in claim 5, spraying amount per tablet in the sampling chamber of the tablet production method described in any one of clams 1 - 4 is defined greater than or equal to 0.000 1 weight percent and less than or equal to 0.2 weight percent.

[0063] The amount of lubricant is preferably reduced as far as possible in order to prevent disintegration time of tablet from extending and to prevent hardness of tablet from lowering. The amount of lubricant per tablet is preferably greater than or equal to 0.0001 weight % and less than or equal to 0.2 weight %, more preferably greater than or equal to 0.01 weight % and less than or equal to 0.1 weight %.

[0064] According to this production method, lubricant amount per tablet is set greater than or equal to 0.0001 weight % and less than or equal to 0.2 weight %. Therefore disintegration time of tablet doesn't extend and hardness of tablet doesn't deteriorated.

[0065] According to the tablet production method as set forth in claim 6, the punches described in any one of clams 1 - 5 are provided with a projected line for forming a dividing line of a tablet.

[0066] In this tablet production method, the punches are provided with a projected line for forming a dividing line of a tablet so that a dividable tablet including powdered or granular compound which is denaturalized or inactivated when tabletted at high pressure and a dividable tablet including solid dispersion powdered or granulated of which function isn't damaged.

[0067] The tablet production method in claim 7 is characterized in that the following steps as set forth in claim 1 or 2 are continuously executed; housing the punches and the dies in the sampling chamber; generating pulsating vibration air, spraying lubricant mixed in air in the spraying chamber, and applying the lubricant on the surfaces of the punches and the dies while the lubricant sprayed in the spraying chamber is mixed with the pulsating vibration air, and tabletting the molding material by means of the punches applied with the lubricant on the surface thereof and the dies applied with the lubricant on the surface thereof.

[0068] According to this method, tabletting is continuously executed utilizing the fact that sticking isn't caused. A tablet including compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure can be produced at industrial production base.

[0069] The tablet production method in claim 8 is characterized in that the following procedures as set forth in claim 3 or 4 are continuously executed; housing the punches and the dies in the spraying chamber; applying the lubricant on the surfaces of the punches and the dies while the lubricant sprayed in the spraying chamber is mixed with the positive pulsating vibration air; and tabletting the molding material by means of the punches applied with the lubricant on the surface thereof and the dies applied with the lubricant on the surface thereof.

[0070] According to this method, tabletting is continuously executed utilizing the fact that sticking isn't caused. A tablet including solid dispersion powdered or granulated can be produced at industrial production base.

[0071] The tablet production method in claim 9 is characterized in that tabletting pressure for the molding compound by means of the punches applied with the lubricant on the surface thereof and the dies applied with the lubricant on the surface thereof is low in the method as set forth in any one of clams 1 - 8.

[0072] Herein "low pressure" means that tabletting pressure is lower comparing with the prior internal lubricant method and the prior external lubricant spraying method. More concretely explained, this tablet production method can produce a tablet having enough practical level hardness even if its tabletting pressure is less than or equal to 1 ton/cm^2.

[0073] According to this tablet production method, tabletting pressure for molding material is low. Even if the granule included in the tablet is powdered or granular material including compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure, such material can be tabletted without denaturalizing or deactivating the compound.

[0074] Further, even if granule to be included in the tablet is solid dispersion powdered or granulated, such material can be tabletted without destroying the function thereof.

[0075] The tablet described in claim 10 includes granule containing active agent in diluting agent and lubricant only on the surface thereof and the granule is compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure.

[0076] The tablet has lubricant only on the surface thereof so that delay of tablet disintegration time, which is caused by water repellency of lubricant, isn't happened.

[0077] Further, this tablet includes lubricant therein so that it can be tabletted at low tabletting pressure. As a result, compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure isn't denaturalized or inactivated.

[0078] The tablet as set forth in claim 11 includes granule containing active agent in diluting agent and lubricant only on the surface thereof, and the granule is solid dispersion powdered or granulated.

[0079] Such a tablet is provided with lubricant only on its surface so that disintegration time of the tablet, which may be caused by repellency of lubricant, doesn't delay.

[0080] Further, the tablet doesn't include lubricant therein so that it can be tabletted at low pressure and the function of solid dispersion powdered or granulated isn't damaged.

[0081] According to the tablet described in claim 12, the lubricant amount per tablet as set forth in claim 10 or 11 is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent.

[0082] Such a tablet is provided with minute amount of lubricant on its surface so that disintegration time delay of the tablet, which may be caused by repellency of lubricant, doesn't happen.

[0083] Therefore, when this tablet is used as an uncoated tablet, it becomes a rapidly soluble tablet. It is desirable when a tablet is required to be rapidly disintegrated at an objected place like an intraorally rapidly disintegrable tablet. Further, if the tablet surface is coated with a film which is dissolved at the objective place, the tablet is rapidly dissolved at the objective place when the coated film is dissolved so that such a tablet can be preferably used as a tablet expected to be dissolved at the objective place.

[0084] The tablet in claim 13 is characterized in that the shape of the tablet as set forth in any one of clams 10 - 12 is anomalous.

[0085] "Anomalous" in this specification means shapes except for round, for example, track (capsule), rugby ball, polygon such as triangle, rectangle, pentagon, and so on, diamond, almond, bombshell, half moon, heart, star, and so on.

[0086] Because a tablet has anomalous shape, contained drugs (active agent) can be easily distinguished according to these shapes. As a result, such a tablet doesn't have a fear of medication error.

[0087] The tablet in claim 14 is characterized in that the tablet as set forth in any one of clams 10 - 13 has a dividing line on the surface thereof.

[0088] According to such a tablet, a tablet which is soluble at a desired place and is also dividable can be provided in the market.

Brief Description of Drawings

[0089]

Fig.1 schematically shows a sectional view of an enlarged substantial part of one embodiment of an external lubricant spraying type tabletting machine used in the tablet production method of the present invention.

Fig.2 is a schematic section of the external lubricant spraying type tabletting machine shown in Fig.1.

Fig.3 schematically shows a substantial part of the external lubricant spraying type tabletting machine shown in Fig.1. Fig.3(a) is a schematic section of the external lubricant spraying type tabletting machine according to the present invention. Fig.3(b) is a schematic section around the pulsating vibration air generation means.

Fig.4 explains a concrete example of pulsating vibration air, Fig.4(a) and Fig.4(b) show negative pulsating vibration air respectively.

Fig.5 schematically shows other embodiment of the external lubricant spraying type tabletting machine used for the tablet production method of the present invention. Fig.5(a) is a schematic section of an enlarged substantial part of the external lubricant spraying type tabletting machine of the present invention and Fig.5(b) is a schematic sectional view around pulsating vibration air generation means.

Fig.6 explains a concrete example of pulsating vibration air. Fig.6(a) and Fig.6(b) show positive vibration air respectively.

Fig.7 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig. 8 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.9 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.10 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.11 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.12 schematically shows a sectional view of means (metering feeder) for quantitatively supplying molding lubricant contained in a hopper into a conduit.

Fig. 13 is a plane view schematically showing one embodiment of an elastic membrane used for the means (metering feeder) in Fig.12.

Fig.14 schematically shows operations of the means (metering feeder) shown in Fig.12.

Fig.15 is a plane view schematically showing another embodiment of an elastic membrane used for the means (metering feeder) in Fig.12.

Fig.16 is a sectional view schematically showing another embodiment of pulsating vibration air generation means.

Fig.17 schematically shows procedures of the prior tablet production method disclosed in JP-B-41-11273.

Fig.18 schematically shows procedure of the prior tablet production method disclosed in JP-A-56-14098.

Disclosure of the Invention

[0090] The tablet production method according to the present invention will be detailed hereinafter referring to the attached drawings.

[0091] Here the present invention will be explained when a rotary type tabletting machine is used.

[0092] Fig.1 shows schematic construction by enlarging one part around a rotary table of a rotary type tabletting machine used for executing the present invention.

[0093] Fig.2 is a schematic section when one part of Fig.1 around the rotary table is enlarged.

[0094] As shown in Fig.1 and Fig.2, the rotary type tabletting machine A is comprised of a rotatably provided rotary table 2 having plural dies 1, • • • in circumferential direction, plural upper punches 3, • • • and plural lower punches 4, • • • provided so as to correspond to each dies 1, • • • . A spraying chamber 8 is provided at P1 which is before a point P2 where molding material is charged in the die 1. A pulsating vibration air generation means 7 is connected to the spraying chamber 8 and a spray nozzle 9 for spraying lubricant L is provided in the spraying chamber 8. In this embodiment, an air source 10 such as a cylinder charging compressed air is connected to the spray nozzle 9 and lubricant L is designed to be sprayed from the spray nozzle 9 by the air generated from the source 10.

[0095] Next, tablet production procedure using this machine A will be explained.

[0096] The rotary table 2 is rotated at a fixed speed, pulsating vibration air is generated in the spraying chamber 8 by driving the pulsating vibration air generation means 7 when the die 1 comes to the point P1 where the spraying chamber 8 is provided according to rotation of the rotary table 2, lubricant L is simultaneously sprayed from the spray nozzle 9, and lubricant L is applied on an inner wall 1s of the die 1, a lower surface 3s of the upper punch 3, and an upper surface 4s of the lower punch 4.

[0097] Then, molding material m is charged in the die 1 which comes to the point P2 for charging molding material m in the die 1 accompanied with rotation of the rotary table 2 and extra molding material m is removed. Thereafter, when the die 1 charged with molding material m comes to a point P3 for compressing molding material m, molding material m in the die 1 is compressed to produce a tablet by means of the upper punch 3 of which lower surface 3s is applied with lubricant L and the lower punch 4 of which upper surface 4s is applied with lubricant L. Further, when the die 1 comes to a point P4, a tablet T is discharged from the die 1 so that the tablet T is produced.

[0098] Fig.3 (a) shows schematic construction around the spraying chamber 8 and Fig.3(b) illustrates construction by an example of pulsating vibration air generation means 7.

[0099] In this example, the pulsating vibration air generation means 7 is connected to the spraying chamber 8 via a conduit 13.

[0100] In Fig.3(b) the numeral 71 shows a blower, 72 shows a cylindrical tube, 73 shows a valve element provided rotatably around a rotary axis 74 so as to divide inside of the tube 72 into two parts. The conduit 13 and a conduit 14 coupled to the blower 71 are connected at a given place of the side of the tube 72. The valve element 73 is designed to be rotated at a desired rotational velocity by means of a valve rotation control means (not shown).

[0101] When the blower 71 is rotated at a given rotation number and the valve element 73 is also rotated at a given rotation number, the spraying chamber 8 and the blower 71 are connected as the valve element 73 is positioned at a place shown by a solid line in the figure. When the valve element 73 is positioned at a place shown by a dotted line, the spraying chamber 8 and the blower 71 are blocked off by the valve element 73. Accordingly, pulsating vibration air with its peak at atmospheric pressure and its valley at negative pressure shown in Fig. 4(a) or pulsating vibration air with its peak and valley at negative pressure shown in Fig.4(b) can be produced in the spraying chamber 8.

[0102] Here "negative pressure" means that the pressure in the spraying chamber 8 is lower than outside pressure (atmospheric pressure).

[0103] According to this tablet production method, because lubricant L isn't included in the molding material m, produced tablet can obtain practical hardness even if tabletting pressure is less than or equal to 1 ton/cm^2. Therefore, this

method is suitable for producing a tablet including compound which is denaturalized or inactivated when tabletted at high pressure and a tablet including solid dispersion powdered or granulated.

[0104] When lubricant L is sprayed from the spray nozzle 9 while generating pulsating vibration air shown in Fig.4(a) or Fig.4(b), sprayed lubricant L is diffused by the pulsating vibration air and attaches on the inner wall is of the die 1, the lower surface 3s of the upper punch 3 and the upper surface 4s of the lower punch 4 both of which are provided so as to correspond to the die 1 housed in the spraying chamber 8.

[0105] According to this tablet production method, as lubricant L can be uniformly applied on the inner wall is of the die 1, the lower surface 3s of the upper punch 3, and the upper surface 4s of the lower punch 4, molding material m can be prevented from adhering on the die 1, the upper punch 3, and the lower punch 4 of the tabletting machine A even if the amount of lubricant L sprayed in the spraying chamber 8 is only a little.

[0106] Utilizing this, if the spray amount of lubricant L to be sprayed in the spraying chamber 8 is controlled to be greater than or equal to 0.0001 weight % and less than or equal to 0.2 weight % per the weight of tablet, a part of lubricant L attached on the inner wall is of the die 1, the lower surface 3s of the upper punch 3, and the upper surface 4s of the lower punch 4 is slightly attached only on the surface of the produced tablet T so that the tablet T without including lubricant L therein can be produced.

[0107] As the result, the used amount of lubricant L for the tablet T is remarkably small comparing with the tablet produced by the prior production method. Therefore, a problem, which has been found in the prior tablet, wherein disintegration time of tablet delays because of water repellency of lubricant L is never happened.

[0108] Accordingly, if the tablet T produced according to the above-mentioned method is used as an uncoated tablet, it becomes a rapidly soluble tablet and is suitable as a tablet which is required to be rapidly disintegrated at an objected part like an intraorally rapidly disintegrable tablet.

[0109] If a film coat which can be melted at an objective part is executed on the surface of the tablet, the tablet is rapidly dissolved at an objective part when the film coat is melted. Consequently, a tablet which can be dissolved at an objective part can be produced.

[0110] In this embodiment, the system shown in Fig.3(b) is used as a pulsating vibration air generation means 7, however, it is only an example and any kinds of system can be used as the pulsating vibration air generation means 7. For example, the blower 71 may be connected to the end of the conduit 13, a solenoid valve may be provided in the middle of the conduit 13 for opening and closing the conduit 13, the blower 71 may be rotated at a given rotation number so as to suck air in the spraying chamber 8, and the conduit 13 may be opened or closed at a prescribed period by the solenoid valve. Otherwise the blower 71 may be connected to the end of the conduit 13, the blower 71 may be rotated fast or slowly at a given period, and air in the spraying chamber 8 may be sucked strongly and weakly.

[0111] Also in the above-mentioned embodiment, the pulsating vibration air shown in Fig.4(a) or Fig.4(b) is generated. The system shown in Fig.5 may be constructed and the pulsating vibration air shown in Fig.6(a) or Fig.6(b) may be generated in the spraying chamber 8. Namely, in the embodiment shown in Fig.5, a pulsating vibration air generation means 7A is connected to the end of the conduit 13, a hopper 15 storing lubricant L is connected in midstream of the conduit 13, and a compressed air generation means 16 such as a cylinder charging compressed air is connected to the hopper 15 as shown in Fig. 5(a). The numeral 17 in Fig. 5(a) shows a blower provided if required. When the blower 17 is driven, air in the spraying chamber 8 is sucked and pulsating vibration air supplied in the spraying chamber 8 and lubricant L are induced to be discharged from the spraying chamber 8.

[0112] As shown in Fig.5(b), the pulsating vibration air generation means 7A is provided with the blower 71, the cylindrical tube 72 connected to the conduit 13 between the blower 71 and the hopper 15, and the valve element 73 which is rotatable around the rotary axis 74 in the tube 72 and is designed to divide the inside of the tube 72 into two parts. The conduit 13 and the conduit 14 coupled to the blower 71 are connected to the side of the tube 72. The valve element 73 is constructed so as to be rotated at a desired rotational velocity by means of a valve rotation control means (not shown).

[0113] When the blower 71 is rotated at a given rotation number to send air to the spraying chamber 8 and the valve element 73 is also rotated at a given rotational velocity, the spraying chamber 8 and the blower 71 are connected when the valve element 73 is located at the place shown as a slid line in the figure. When the valve element 73 is located at a dotted line, the spraying chamber 8 and the blower 71 are blocked off by the valve element 73. Accordingly pulsating vibration air with its peak at positive pressure and its valley at atmospheric pressure as shown in Fig.6(a) is generated in the spraying chamber 8. Otherwise, pulsating vibration air with its peak and valley at positive pressure as shown in Fig.6(b) may be generated in the spraying chamber 8. While keeping this condition, the compressed air generation means 16 may be driven to feed lubricant L contained in the hopper 15 to the conduit 13 and a fixed amount of lubricant L may be supplied in the spraying chamber 8 together with the current of pulsating vibration air.

[0114] Here positive pressure means that the pressure in the spraying chamber 8 is higher than the pressure outside of the spraying chamber 8 (atmospheric pressure).

[0115] Otherwise, the blower 71 may be provided at the end of the conduit 13, the solenoid valve for opening and closing the conduit 13 may be also provided in the midstream of the conduit 13, the blower 71 may be rotated at a given

rotation number to feed air in the spraying chamber 8, the conduit 13 may be opened and closed periodically, then pulsating vibration air may be generated in the spraying chamber 8 and the conduit 13. While keeping such a condition, the compression air generation means 16 may be driven to feed lubricant L contained in the hopper 15 to the conduit 13 and a fixed amount of lubricant L is supplied in the spraying chamber 8 together with the current of pulsating vibration air. On the other hand, the blower 71 may be connected at the end of the conduit 13, the blower 71 may be rotated fast or slowly at a given period so as to feed air strongly or weekly in the spraying chamber 8, and pulsating vibration air may be generated in the spraying chamber 8 and the conduit 13. While keeping this condition, the compression air generation means 16 may be driven so as to feed lubricant L contained in the hopper 15 to the conduit 13 and a fixed amount of lubricant L may be supplied in the spraying chamber 8 together with the current of pulsating vibration air.

[0116] The present invention will be further explained based on concrete experimental data.

(Experiment 1)

[0117] Here an example of producing tablet including powdered or granular compound which is denaturalized or inactivated when tabletted at high pressure is shown.

[0118] Water solution of 15w/v% lactose was mixed with water solution of 10w/v% serrapeptase in a ratio of 100g serrapeptase to 50g lactose. The mixture was frozen and dried under the condition wherein initial temperature at -55°C and pressure at 10^{-3}mmHg; final temperature after 27 hours at +60°C and pressure at 10^{-1}mmHg and then mixed, kneaded, dried, and sized. The powdered or granular material (average particle size : 60μm) of which prescription is shown in table 1 is prepared.

Table 1

combined ingredient	Prescription (mg)
serrapeptase	5 mg
lactose	87 mg
cornstarch	37.5 mg
isopropanol	0.015 ml

[0119] Then using the rotary tabletting machine A provided with the pulsating vibration air generation means 7 shown in Fig.1, material was continuously tabletted by means of 7mm diameter die and punch set at a rotational velocity which rotates the rotary table 2 at 30 times per minute so as to produce the sized granulated material of 130mg/tablet.

[0120] Magnesium stearate was used as lubricant and the used amount of magnesium stearate sprayed in the spraying chamber 8 was controlled such that weight % of the lubricant included per a produced tablet becomes 0.03 weight %.

[0121] HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as a main body of the tabletting machine A.

[0122] When the rotary type tabletting machine A provided with the pulsating vibration air generation means 7 shown in Fig.1 was used, it was found that the produced tablet has practical hardness at a tabletting pressure of 0.7 ton/cm^2.

[0123] The condition of pulsating vibration air isn't specifically limited. However, in this experiment, the period of pulsating vibration air was greater than or equal to 1Hz and less than or equal to 10Hz, its valley became 15% - 5% lower than atmospheric pressure and also its peak became almost the same as or a little lower than atmospheric pressure.

(comparison 1)

[0124] Magnesium stearate was added as lubricant for the powdered or granular material used in the experiment 1 as shown in table 1 in a ration of 0.8 weight % for the entire amount of a tablet. After they were well mixed by a V type mixer, they were continuously tabletted by an internal lubricant method at a speed of rotating the rotary table at 30 times per minute by means of a set of 7mm punch and die so as to produce the material into a 130mg tablet.

[0125] HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as the tabletting machine A.

[0126] In this case it was found that the produced tablet didn't have practical hardness at a tabletting pressure of 0.7 ton/cm^2.

(comparison 2)

[0127] The powdered or granular material used in the experiment 1 as shown in table 1 was tabletted by means of a set of 7mm punch and die so as to produce a 130mg tablet. Stearate magnesium was applied on the surfaces of the punch and die according to the method described in JP-B-41-11273 so that the weight % of lubricant became 0.03 weight % per a produced tablet. Then the material was continuously tabletted at a speed of rotating the rotary table 30 times per minute.

[0128] HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as the tabletting machine A.

[0129] Next, disintegration test according to Japanese Pharmacopoeia was executed for three kinds of tablets produced according to the experiment 1, the comparison 1, and the comparison 2 at a given test number (N=5).

[0130] The result is shown in Table 2.

Table 2

	Tabletting Pressure (ton/Cm^2)	hardness (kg)	disintegration, time	
			average measurement (standard variation)	actual measurement
experiment 1	0.7	7	3.0 (±0.2)	3.0
				2.7
				2.9
				3.2
				3.1
comparison 1	0.7	4	7.2 (±0.9)	7.2
				7.8
				8.3
				6.4
				6.2
comparison 2	0.7	7	4.0 (±0.6)	4.1
				3.5
				3.3
				4.8
				4.5

[0131] According to the table 2, it was found that the experiment 1 had high hardness comparing with the comparison 1 and had short disintegration time comparing with the comparison 1 and 2. And also its disintegration time doesn't widely vary.

(comparison 3)

[0132] Magnesium stearate was added as lubricant for the powdered or granular material used in the experiment 1 as shown in the table 1 in a ratio of 0.8 weight % for the entire amount of a tablet. After they were well mixed by a V type mixer, they were continuously tabletted by an internal lubricant method at a speed of rotating the rotary table 30 times per minute by means of a set of 7mm punch and die so as to produce a 130mg tablet.

[0133] In this case a tabletting pressure was 1.3 ton/cm^2 so that produced tablet has practical hardness.

[0134] Next, residual ratio of serrapeptase was measured for the experiment 1, the comparison 1, and the comparison 2. The result was the experiment 1 > the comparison 1 > and the comparison 2.

[0135] Concretely explained, after the tablet including serrapeptase obtained in the experiment 1, the comparison 1, and the comparison 2 were preserved at 40°C for three months, residual ratio of serrapeptase was measured. The residual ratio of the experiment 1 was 98.8%, that of the comparison 1 was 90.7%, and that of the comparison 2 was

87.9%. Accordingly, the tablet including serrapeptase produced according to the present invention had higher stability comparing with the tablet including serrapeptase produced according to the prior invention.

[0136] For each experiment 1, comparisons 1 - 3, material was continuously tabletted for 5 hours and produced tablet was sampled with time. Time which didn't cause sticking was measured by smoothness of produced tablet surface. In the experiment 1, sticking wasn't happened after 5 hours. However, in the comparison 1 and 3 sticking was happened after 1 hour and in the experiment 2 sticking was happened after 2 hours.

[0137] Based on the above-mentioned results, a tablet produced according to the present invention can achieve practical hardness even if tablet is produced at a tabletting pressure less than or equal to 1 ton/cm^2. Therefore, when the present tablet production method is applied for producing tablet including drugs having inferior stability (for example activity is deteriorated), the present invention can heighten stability of drugs included in tablet comparing with the tablet produced according to the prior art (for example there is no problem such as deteriorating activity of drugs included in tablet).

[0138] Therefore, for example, when the tablet including many drugs as shown in tables 3 - 5 is produced, the tablet production method according to the present invention is effective.

Table 3

1.Antipyretics, Analgesics, Antiinflammatory agents	Indometacin,Dicrofenac sodium,Ibuprofen,Asprin, Dexamethasone,Prednisolone,Loxoprofen sodium, Ketoprofen,Serrapeptase,Lysozyme Chloride, Streptokinaze, Salicylamide
2.Antacid, Antiulcers	Famotidine, Sucralfate,Cimetidine,Aceglutamide aluminium,Dried aluminium hydroxide gal,Sodium bicarbonate,Diastase,Sodium copper chlorophyllin, L-glutamine,Sodium alginate
3.Antihypertensives, Cardiovascular agents	Benidipine hydrochloride,nifedipine,nicardipine hydrochloride, amlodipine besylate
4.Antibiotics	Amoxicillin,Ampicillin,Minocycline hydrochloride,
5.Antitussives, Antiasthma agents, Bronchodialators	Theophylline,Methlyephedrine hydrochloride,Sodium cromoglicate,Salbutamol sulfate, Codeine phosphate
6.Diuretics	Furosemide,Chlorothiazide,Spironolactone
7.Tranquilizers	Diazepam,Chlorpromazine,Haloperidol,Bromperidol, Risperidone
8.Antipodagrics	Allopurinol,Probenecid
9.Anticoagulants	Warfarin,Heparin sodium,Alteplase,Urokinase tisokinase
10.Blood coagulants	Blood coagulant factor VIII, Active prothombine complex
11.Erythropoletins	Epoetin β ,Epoetin α
12.Hypolipidemics	Pravastatin sodium,Simvastatin,Bezafibrate, Tocopherol nicotinate,Dextran sulfate sodium
13.Cerebral vasodilators, Peripheral vasodilators	Nicergol,Ibudilast,Citicoline,Flunarizine hydrochloride
14.Calcitonins	Elcatonin,Salmon calcitonin(synthetic)
15.Anticonvulsants	Phenytoin,Sodium propyl valerate,Carbamazepine, Zonisamide

Table 4

16.Antiemetics	Metoclopramide,Donpridone,Cisapride
17.Expectorants	Bromhexine hydrochloride,Carbocisteine, Cysteine ethylester hydrochloride, Ambroxol hydrochloride
18.Antidiabetes	Glibenclamide,Tolbutamide,Insulin, Glucagon-like insulintropic peptide
19.Cardio vascular agents	Ubidecarenon,ATP-2 sodium,Nitroglycerin, Isosorbide didinirate
20.Vitamins	Vitamin A,Vitamin B,Vitamin C,Vitamin D, Folic acid
21.Antipollakisurias Antiduretic hormones	Flavoxate hydrochloride,Oxybutynin hydrochloride, Desmopressin acetate, Vasopressin
22.Ace inhibitors	Enalapril maleate,Alacepril
23.Antiparkinsonism	Droxidopa,Pergolide mesilate,levodopa,carbidopa
24.Digestives	Pancreatic digestive enzyme,Sanactase combined drug,Gastric mucosa extraction drug,Tilactase
25.Anticancer agents	Tegaful,Fluorouracil,Doxifluridine, Methotrexate,Etoposide,Vindesine sulfate, Epirubicin hydrochloride,L-asparaginase, Leuprorelin acetate,Goserelin acetate, Chlormadinone acetate,Tamoxifen citrate, Filgrastim,Lenograstim,nartograstim,Lentinan, Interferon
26.Immunosuppressor	Cyclosporin,Mizoribine,Immunoglobulin
27.Anesthesias	Lidocaine hydrochloride,Procaine hydrochloride, morphine sulfate,Buprenorphine hydrochloride, Pentazocine,Fentanyl
28.Sedatives	Brotizolam,Triazolam,Flunitrazepam, Flurazepam hydrochloride
29.Nootropics	Idebenone,Propentofylline, Indeloxazine hydrochloride, Bifemelane hydrochloride,

Table 5

30.Antiallergies	Beclometasondipropionat,Ketotifen fumarate, Amlexanox,Terfenadine,Azelastin hydrochloride, Tranist,Olopatadine,Oxatomide,Epinastine hydrochloride,Astemizole
31.Diagnostics, Other therepeutic agents	[^{13}C]Urea,Glucagon,Partially hydolyzed starch, Prostaglandin,Leukotriene,Thromboxan A2, Platelet activating factors,insulinnoid growth factors,Neurone growth factors,Epidermal growth factors,Vascular endothelial growth factors, Ribonucleic acid,Deoxyribonucleic acid, Oligonucleoside,Ttrehalose,Dextran, Chitin,Acacia,Agar,Chondroitin sulfuric acid, Hyaluronic acid,Cyclodextrin,β glucan,Trypsin, Chymotrypsin,Pepsin,Aprotinin,Bestatin, Mumpsvaccine,Poliovaccine

[0139] Further, it was found that sticking and so on were hardly caused when tabletting.

(Experiment 2)

[0140] Here an example of producing a tablet including solid dispersion powdered or granulated.

[0141] 2500g of hydroxypropylmethylcellulose acetate succinate (brand name : A coat, AS-MP, Shinetsu Kagaku Kogyo Co., Ltd.) was mixed with 500g of original powder (average particle size : 60μm) made by grinding donperidone. Thereafter, processing treatment was executed by means of a dual axis extruder equipped with dies of 4mmϕ×2 caliber (KEX-25:Kurimoto Tekkosho Co., Ltd.) at 100°C barrel temperature at extruding speed of 200rpm while adding a little water, thereby solid dispersion was obtained.

[0142] Thus obtained solid dispersion was minutely ground by a sample mill (type : AP-S, Hosokawa Tekkosho Co., Ltd.).

[0143] Next, such solid dispersion was tabletted by a tabletting machine with an external lubricant spraying means A as follows. The punches 3, 4 and the die 1 were housed in the spraying chamber 8, magnesium stearate was applied as lubricant L on the surfaces of 3s, 4s of the punches 3, 4 and the surface 1s of the die 1 by generating pulsating vibration air as shown in Fig.4(a) in the spraying chamber 8. The substance was continuously tabletted by means of the punches 3, 4 and the die 1 on which surfaces 3s, 4s, 1s were applied with magnesium stearate at a speed of rotating the rotary table at 30 times per minute.

[0144] The conditions of pulsating vibration air isn't limited. However in this example, period of pulsating vibration air was more than or equal to 1Hz and less than or equal to 10Hz, the valley thereof was set at about 10% lower than atmospheric pressure, and the peak thereof was equal to or a little less than atmospheric pressure.

[0145] Next, solubility test of thus obtained tablet of solid dispersion and powder X-ray diffraction test (250 mesh passing) were executed.

(comparison 4)

[0146] 2500g of hydroxypropylmethylcellulose acetate succinate (brand name : A coat, AS-MP, Shinetsu Kagaku Kogyo Co., Ltd.) was mixed with 500g of original powder (average particle size : 60μm) made by grinding donperidone. Thereafter, processing treatment was executed by means of a dual axis extruder equipped with dies of 4mmϕ×2caliber (KEX-25:Kurimot Tekkosho Co.,Ltd.) at 100°C barrel temperature at extruding speed of 200rpm while adding a little water, thereby solid dispersion was obtained.

[0147] Thus obtained solid dispersion was minutely ground by a sample mill (type : AP-S, Hosokawa Tekkosho Co., Ltd.) and solubility test of thus obtained minute particle and powder X-ray diffraction test (250 mesh passing) were executed.

[0148] As a result, the experiment 2 and the comparison 4 showed almost the same solubility and it was found that crystal peak of donperidone of both cases were disappeared.

[0149] For the experiment 2 and the comparison 4, material was continuously tabletted for 5 hours and tablets were sampled with time, then time without happening sticking was measured by smoothness of the produced tablets. Sticking wasn't seen after 5 hours in the experiment 2, however in the comparison 4, sticking was already seen after 1 hours.

[0150] Several kinds of solid dispersion was produced for the several drugs shown in the tables 3 - 5 by means of a dual axis type extruder and similar tests as the experiment 2 and the comparison 4 were executed.

[0151] The punches 3, 4 and the die 1 were housed in the spraying chamber 8, magnesium stearate was applied as lubricant L on the surfaces of 3s, 4s of the punches 3, 4 and the surface 1s of the die 1 by generating pulsating vibration air as shown in Fig.4(a) in the spraying chamber 8. The substance was continuously tabletted by means of the punches 3, 4 and the die 1 on which surfaces 3s, 4s, 1s were applied with magnesium stearate at a speed of rotating the rotary table at 30 times per minute. It was found that thus obtained tablet and minute particles obtained by grinding the solid dispersion by a sample mill had almost the same solubility and crystal peak of both of them were disappeared.

[0152] According to the above-mentioned results, it was found that the tablet production method according to the present invention could be preferably used for producing a tablet of solid dispersion.

[0153] Next, several anomalous tablets shown in Fig.7 - 11 were produced similar to the experiment 1, 2, however a punch and a die comprising a female mold of tablet.

[0154] The tablet in Fig.7(a) shows a circular tablet generally called flat plain, the tablet in Fig.7(b) shows a circular tablet generally called shallow concave plain, the tablet in Fig.7(c) shows a circular tablet generally called normal concave plain, the tablet in Fig.7(d) shows a circular tablet generally called deep concave plain, tablet in Fig.7(e) Shows a circular tablet generally called ball or pill, tablet in Fig.7(f) shows a circular tablet generally called flat beveled edge.

[0155] The tablet in Fig.8(a) shows a circular tablet generally called double radius, the tablet in Fig.8(b) shows a circular tablet generally called bevel and concave, the tablet in Fig. (8c) shows a circular tablet generally called ring, the tablet in Fig.8(e) shows a a circular tablet generally called rim, and the tablet in Fig.8(f) shows a capsule type tablet generally called capsule.

[0156] The tablet in Fig.9(a) shows a circular tablet generally called oval, the tablet in Fig.9(b) shows an elliptical tablet generally called ellipse, the tablet in Fig.9(c) shows a rectangular tablet generally called square, the tablet in Fig.9(d) shows a triangular tablet generally called triangle, the tablet in Fig.9(e) shows a pentangular tablet generally called pentagon, and the tablet in Fig.9(f) shows a hexagonal tablet generally called hexagon.

[0157] The tablet in Fig.10(a) shows a heptagonal tablet generally called heptagon, the tablet in Fig.10(b) shows a octagonal tablet generally called octagon, the tablet in Fig.10(c) shows a diamond-shapedtablet generally called diamond, the tablet in Fig.10(d) shows a pillow-shaped tablet generally called pillow or barrel, the tablet in Fig.10(e) shows a rectangular tablet generally called rectangle, and the tablet in Fig.10f) shows an almond-shaped tablet generally called almond.

[0158] The tablet in Fig.11(a) shows a sagittal tablet generally called arrow head, the tablet in Fig.11(b) shows a bullet-shaped tablet generally called bullet, the tablet in Fig.11(c) shows a semilunar tablet generally called half moon,

the tablet shown in Fig.11(d) shows a shell-shaped tablet generally called shelled, the tablet in Fig.11(e) shows a heart-shaped tablet generally called heart, and the tablet in Fig.11(f) shows a star-shaped tablet generally called star.

[0159] Material was continuously tabletted for 5 hours by means of punches and dies comprising a female mold for the tablets shown in Fig.7- Fig.11, obtained tablets were sampled with time, and time for causing sticking was measured by smoothness of the produced tablet's surface. The result was that sticking wasn't happened even after 5 hours.

[0160] From the above-mentioned results, it was found that the tablet production method according to the present invention can be preferably used for producing anomalous tablets Other than circular tablets.

[0161] For tablets using an engraved mark or a dividing line, several dividable tablets were produced like the experiments 1 and 2 except that punches with a projected line for forming a dividing line were used.

[0162] Material was continuously tabletted for 5 hours, the produced tablets were sampled with time, and time for happening sticking was measured by smoothness of tablets' surfaces. Sticking wasn't seen even after 5 hours.

[0163] Negative pulsating vibration air was used in the above-mentioned experiments. However, pulsating vibration air isn't limited to negative one. When positive pulsating vibration air is used, similar result can be obtained.

[0164] In this case, conditions of positive pulsating vibration air aren't specifically limited. The period may be more than or equal to 1Hz and less than or equal to 10Hz, its peak may be 10% - 15% higher than atmospheric pressure, and its valley may be almost equal to or a litter higher than atmospheric pressure.

[0165] In the disclosure of the invention, a system wherein the hopper 15 is connected in midway of the conduit 13 and the compressed air generation means 16 such as a cylinder fully charged with compressed air is connected to the hopper 15 as shown in Fig.5 is explained. However, the system for discharging lubricant L stored in the hopper 15 to the conduit 13 isn't limited to such a system.

[0166] Fig.12 explains such a system schematically.

[0167] According to the system, a pulsating vibration air generation means 7A is connected to one end 13a of the conduit, a discharge port 15a of the hopper 15 is connected in midway of the conduit 13, and an elastic membrane 18 with an aperture (slit in this example) 18a is provided at the discharge port 15a so as to be a bottom of the hopper 15 (see Fig.13).

[0168] The elastic membrane 18 is made of rubber such as silicon rubber.

[0169] The member shown as 15b in the Fig.12 is a lid and is provided for the hopper 15 removably and airtightly.

[0170] Next, operations of the system will be explained.

[0171] Fig.14 is an explanatory figure schematically showing operation of the system.

[0172] For using the system, the lid 15b is airtightly attached on the hopper 15 after lubricant L is contained in the hopper 15.

[0173] Then, when the pulsating vibration air generation means 7A is driven to supply positive pulsating vibration air to the conduit 13, the air pressure in the conduit 13 becomes higher than that in the hopper 15 while positive pulsating vibration air is at peak side. As shown in Fig.14(a), the elastic membrane 18 is deformed with its center curved upwardly in such a manner that the center becomes an antinode and the circumferential edge becomes a node.

[0174] In this case, the section of the aperture (slit in this example) 18a becomes V-shaped with is upper end opened. A part of lubricant L stored in the hopper 15 drops in the V-shaped aperture (slit in this example) 18a.

[0175] As positive pulsating vibration air changes from peak to valley, the air pressure in the conduit 13 is generally lowered so as to be the same as that in the hopper 15. The elastic membrane 18 is going to get back to its original shape because of its resilience as shown in Fig.14(b). The lubricant L dropped in the V-shaped aperture (slit in this example) 18a is caught in the aperture 18a.

[0176] When the positive pulsating vibration air supplied in the conduit 13 is at its valley, the air pressure in the conduit 13 becomes lower than that in the hopper 15 and the elastic membrane 18 is deformed with its center curved downwardly in such a manner that the center is antinode and the circumferential. edge is node.

[0177] In this case, the section of the aperture (slit in this example) 18a becomes reverse V-shaped with its lower end opened. The lubricant L caught in the aperture 18a is discharged to the conduit 13.

[0178] Then the lubricant L discharged in the conduit 13 is immediately mixed with positive pulsating vibration air supplied in the conduit 13 to be dispersed in the conduit 13 and is pneumatically transported to a spraying chamber (refer to the spraying chamber 8 in Fig.5).

[0179] The elastic membrane 18 repeats up and down vibration as shown in Fig.14(a) -Fig.14(c) according to vibration amplitude, wave length, wave shape, and vibration frequency of positive pulsating vibration air.

[0180] Therefore, as long as vibration amplitude, wave length, wave shape, and vibration frequency of positive pulsating vibration air supplied in the conduit 13 are fixed, the elastic membrane 18 vibrates up and down at a fixed vibration amplitude and frequency. Accordingly the amount of lubricant L discharged in the conduit 13 via the aperture (slit in this sample) 18a is constant.

[0181] Further according to this system, because positive pulsating vibration air is supplied in the conduit 13, there are no phenomenon such as adhesion of powdered material on the inner wall of the conduit 13 and blowing-out of powdered material in the conduit 13 which have been seen in the case that steady air pressure is used for pneumatically

transporting powdered material.

[0182] Therefore, according to this system, lubricant L is discharged from the other end 13b of the conduit 13 at the same density as the lubricant L discharged in the conduit 13.

[0183] In other words this system can be functioned as a metering feeder.

[0184] Therefore, when the other end 13b of the conduit 13 is connected to the spraying chamber (refer to spraying chamber 8 in Fig.5), as long as the size of the aperture (slit in this example) 18a is fixed, and vibration amplitude, wave length, wave shape, and vibration frequency of positive pulsating vibration air supplied in the conduit 13 are fixed, lubricant L with constant density can be always supplied in the spraying chamber (refer to spraying chamber 8 in Fig.5).

[0185] Further, a media for pneumatically transporting lubricant L is air even if it is a positive pulsating vibration air so that the amount of lubricant L mixed with positive pulsating vibration air can be extremely minimized.

[0186] Accordingly, because a minute amount of lubricant L can be always sprayed in stable condition in the spraying chamber (refer to spraying chamber 8 in Fig. 5), minute amount of lubricant L can be applied on the surfaces of the punches(the surface (lower surface) 3s of the upper punch and the surface (upper surface) 4s of the lower punch 4 as shown in Fig.2) and the surface (inner wall) 1s of the die 1.

[0187] In Fig.12, the elastic membrane has a slit 18a, however, this is only a preferable example. The aperture provided for the elastic membrane isn't limited to the slit 18a and the aperture may be small ones or the number isn't limited to one.

[0188] When the size and the number of the aperture or conditions (vibration amplitude, wave length, wave shape, and vibration frequency) of positive pulsating vibration air supplied in the conduit 13 are varied, the density of lubricant L supplied in the spraying chamber (refer to the spraying chamber 8 in Fig.5) can be changed diversely.

[0189] In this embodiment, a rotary type pulsating vibration air generation means 7A shown in Fig.3(b) and Fig.5(b) wherein a valve element 73 is provided rotatably around a rotary axis 74 so as to divide inside of the tube 72 into two parts is explained as a pulsating vibration air generation means. However, it isn't limited to such means 7A.

[0190] Fig.16 shows a section of other embodiment of pulsating vibration air generation means.

[0191] The high pressure pulsating vibration air generation means 7B is provided with a valve chamber 94 having a valve seat 94 between an input port 91 and an output port 92 and a valve plug 96 which opens and closes by a cam mechanism 95.

[0192] The cam mechanism 95 is provided with a rotary cam 97 rotatable by a driving means such as a motor (not shown) and a roller 98 attached at the lower end of the valve plug 96.

[0193] The valve seat 93 is formed with a hole narrowing into the output port 92 and the valve plug 96 is formed like a reverse mortar so as to conform to the shape of the valve seat 93 and designed to airtightly close the valve seat 93.

[0194] Further in this embodiment, an axis 96a of the valve plug 96 is provided in an axis hole 99h of a case 99 so as not to leak air and so as to be movably up and down.

[0195] The roller 98 is rotatably pinched by the rotary cam 97 and moves up and down according to a concavo-convex pattern on the rotary cam 97 while rotating.

[0196] More detailed, the rotary cam 97 is provided with an inner rotary cam 97a and an outside rotary cam 97b.

[0197] Concavo-convex pattern is provided for the inner rotary cam 97a and the outside rotary cam 97b respectively so as to keep distance of the roller 98 and to keep in line each other.

[0198] The roller 98 is pinched between the inner rotary cam 97a and the outside rotary cam 97b and is moved up and down while rotating according to the concavo-convex pattern provided for the inner rotary cam 97a and the outside rotary cam 97b by rotating the rotary cam 97 without causing jumping of the valve plug 96.

[0199] The convavo-convex pattern provided for the rotary cam 97 is selected according to physical property of lubricant L stored in the hopper 15.

[0200] In this embodiment, a flow rate control means 102 is provided for the input port 91 and compressed air which is generated by an air source 71 and of which flow rate is adjusted properly by the flow rate control means 102 is supplied in the input port 91.

[0201] Further, one end of a conduit (the conduit 13 shown in Fig.3 or Fig.5) is connected to the output port 92.

[0202] The numeral 100 in Fig.5 shows a flow rate control port provided if required. An output control valve 101 for adjusting pressure of pulsating vibration air generated from the output port 92 is provided so as to be adjustable at a desired condition from full communication to atmospheric air and shut down from atmospheric air.

[0203] Next, operational procedure for generating positive pulsating vibration air having a desired period, vibration amplitude, and wave shape by means of the high pressure pulsating vibration air generation means 7B will be explained.

[0204] The rotary cam 97 which is easy to mix lubricant L with air according to physical property of lubricant L stored in the hopper 15 is attached to a rotary axis Ma of a driving means (not shown) of the high pressure pulsating vibration air generation means 7B.

[0205] Then the air source 71 is driven and a fixed amount of compressed air is supplied to the input port 92 by adjusting the flow rate control means 102.

[0206] Further, the rotary cam 97 is rotated at a fixed rotational velocity by actuating the driving means (not shown).

[0207] The pressure of pulsating vibration air discharged from the output port 92 is adjusted by adjusting the output control valve 101, if required.

[0208] When the rotary cam 97 is rotated at a fixed rotational velocity, the valve plug 96 moves up and down according to the concavo-convex pattern of the rotary cam 97. Therefore, when the valve seat 93 is controlled at full closed, half opened, or full opened according to the concavo-convex pattern of the rotary cam 97, pulsating vibration air with a desired wave shape can be outputted from the output port 92.

[0209] According to the high pressure pulsating vibration air generation means 7B, rotational velocity of the rotary cam 97 may be changed by controlling the driving means (not shown) in order to obtain a desired period of pulsating vibration air discharged from the output port 92. Further, the air source 71, the flow rate control means 102, and/or the output control valve 101 may be appropriately controlled in order to obtain a desired vibration amplitude of pulsating vibration air discharged from the output port 92.

Industrial Applicability

[0210] As mentioned above, according to the tablet production method as set forth in claim 1, as lubricant is sprayed in a spraying chamber generating pulsating vibration air and lubricant mixed with pulsating vibration air is applied on the surfaces of punches and dies, lubricant can be uniformly applied on the surfaces of punches and dies comparing with the prior external lubricant spraying method.

[0211] As a result, in a process of tabletting compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure, compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure is hard to be attached on the surfaces of punches and dies and also sticking, capping, laminating, and so on are hardly happened for the produced tablets of biological pharmaceuticals.

[0212] Further, lubricant is only attached on the surfaces of tablets and isn't included inside therein. So, comparing with the tablet including lubricant therein, when compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure is tabletted at a low tabletting pressure (concretely at tabletting pressure less than 1 ton/c m^2), the produced tablet has practical hardness.

[0213] According to the tablet production method as set forth in claim 2, as lubricant is sprayed in a spraying chamber generating pulsating vibration air and lubricant mixed with pulsating vibration air is applied on the surfaces of punches and dies, lubricant can be uniformly applied on the surfaces of punches and dies comparing with the prior external lubricant spraying method.

[0214] As a result, in a process of tabletting solid dispersion powdered or granulated, molding material is hard to be adhered on the surfaces of punches and dies and also sticking, capping, laminating, and so on are hardly happened for the produced tablets of solid dispersion.

[0215] Further, lubricant is only attached on the surfaces of produced tablets of solid dispersion and isn't included inside therein. So, comparing with the tablet of solid dispersion including lubricant therein, when solid dispersion powdered or granulated is tabletted at a low tabletting pressure, the produced tablet of solid dispersion has practical hardness.

[0216] Therefore, according to this tablet production method, a tablet of solid dispersion can be produced at low tabletting pressure so that physical property of solid dispersion doesn't change.

[0217] According to the tablet production method as set forth in claim 3, as lubricant mixed with positive pulsating vibration air is sprayed in a spraying chamber to be applied on the surfaces of the punches and dies, lubricant can be uniformly applied thereon comparing with the prior external lubricant spraying method.

[0218] As a result, in a process of tabletting compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure, compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure is hard to be attached on the surfaces of punches and dies and also sticking, capping, laminating, and so on are hardly caused for the produced tablets of biological pharmaceuticals.

[0219] Further, lubricant is only attached on the surfaces of tablets and isn't included inside therein. So, comparing with the tablet including lubricant therein, when compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure is tabletted at a low tabletting pressure (concretely at tabletting pressure less than 1 ton/cm^2), the produced tablet has practical hardness.

[0220] According to the tablet production method as set forth in claim 4, as lubricant mixed with positive pulsating vibration air is sprayed in a spraying chamber to be applied on the surfaces of punches and dies, lubricant can be uniformly applied thereon comparing with the prior external lubricant spraying method.

[0221] As a result, in a process of tabletting solid dispersion powdered or granulated, molding material is hard to be adhered on the surfaces of punches and dies and also sticking, capping, laminating, and so on are hardly caused for the produced tablets of solid dispersion.

[0222] Further, lubricant is only attached on the surfaces of produced tablets of solid dispersion and isn't included

inside therein. So, comparing with the tablet of solid dispersion including lubricant therein, when solid dispersion powdered or granulated is tabletted at a low tabletting pressure, the produced tablet of solid dispersion has practical hardness.

[0223] Therefore, according to this tablet production method, tablet of solid dispersion can be produced at low tabletting pressure so that physical property of solid dispersion doesn't change.

[0224] According to the tablet production method as set forth in claim 5, the spraying amount of lubricant per tablet is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent. Therefore, disintegrating time of tablet doesn't extend or its hardness isn't deteriorated.

[0225] According to the tablet production method as set forth in claim 6, as the punches are provided with a projected line for forming a dividing line of a tablet, a dividable tablet including compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure and a dividable tablet including solid dispersion powdered or granulated of which functions aren't damaged can be easily produced.

[0226] According to the tablet production method as set forth in claim 7, as material is continuously tabletted at tabletting procedure by utilizing that sticking and so on aren't happened, a tablet including powdered or granular compound which is denaturalized or inactivated when tabletted at high pressure can be produced at industrial production base.

[0227] According to the tablet production method as set forth in claim 8, as material is continuously tabletted at tabletting procedure by utilizing that sticking and so on aren't happened, tablet including solid dispersing powdered or granular material can be produced at industrial production base.

[0228] According to the tablet production method in claim 9, as the tabletting pressure for molding material is low, even if granule included in a tablet is powdered or granular material including compound which is denaturalized or inactivated when tabletted at high pressure, tablet can be produced without denaturalizing or deactivating the compound.

[0229] Further, if granule included in a tablet is solid dispersion powdered or granulated, a tablet can be produced without destroying functions of solid dispersion powdered or granulated.

[0230] According to the tablet in claim 10, as lubricant is attached only on the surface of the tablet, disintegrating time of the tablet caused by water repellency of lubricant doesn't delay.

[0231] Further, as this tablet doesn't include lubricant therein, it is tabletted at low tabletting pressure. Therefore, compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure isn't denaturalized or inactivated.

[0232] According to the tablet described in claim 11, as lubricant is only attached on the surface of the tablet, delay of disintegrating time of the tablet caused by water repellency of lubricant isn't happened.

[0233] Further, as this tablet doesn't include lubricant therein, it is tabletted at low tabletting pressure. Therefore, functions of solid dispersion powdered or granulated isn't damaged.

[0234] According to the tablet described in claim 12, only a minute amount of lubricant is attached on the surface of the tablet, disintegrating time of the tablet caused by water repellency of lubricant doesn't delay.

[0235] Therefore, if such a tablet (uncoated tablet) is used as an uncoated tablet, it becomes a rapidly soluble tablet. It is suitable as a tablet which is desired to be disintegrated immediately at an objective place. If a film which is dissolved at an objective place is coated on the surface of the tablet, the tablet can be rapidly dissolved at the objective place when the film is melted. Therefore, such a tablet can be used as a tablet which is desired to be dissolved at an objective place.

[0236] According to the tablet as set forth in claim 13, as the shape of the tablet is anomalous, drugs (active agent) included in tablets can be easily distinguished from the shape. As a result, medication error is hardly caused for these tablets.

[0237] According to the tablet as set forth in claim 14, as a dividing line is provided for the surface of the tablet, dividable tablet which can be dissolved at an objective place can be supplied in the market.

Claims

1. A tablet production method for compressing molding material by means of punches and dies, comprising;

   using powdered or granular material including compound which is denaturalized or inactivated when tabletted at high pressure as said molding material,
   housing said punches and said dies in a spraying chamber,
   generating pulsating vibration air and spraying lubricant mixed in air in said spraying chamber,
   applying the lubricant on the surfaces of said punches and said dies while the lubricant sprayed in said spraying chamber is mixed with said pulsating vibration air, and
   tabletting said molding material by means of said punches applied with said lubricant on the surface thereof and said dies applied with said lubricant on the surface thereof.

2. A tablet production method for compressing molding material by means of punches and dies, comprising;

using solid dispersion powdered or granulated as said molding material,
housing said punches and said dies in a spraying chamber,
generating pulsating vibration air and spraying lubricant mixed in air in said spraying chamber,
applying the lubricant on the surfaces of said punches and said dies while the lubricant sprayed in said spraying chamber is mixed with said pulsating vibration air, and
tabletting said molding material by means of said punches applied with said lubricant on the surface thereof and said dies applied with said lubricant on the surface thereof.

3. A tablet production method for compressing molding material by means of punches and dies, comprising;

using powdered or granular material including compound which is denaturalized or inactivated when tabletted at high pressure as said molding material,
housing said punches and said dies in a spraying chamber,
applying the lubricant on the surfaces of said punches and said dies while the lubricant sprayed in said spraying chamber is mixed with positive pulsating vibration air, and
tabletting said molding material by means of said punches applied with said lubricant on the surface thereof and said dies applied with said lubricant on the surface thereof.

4. A tablet production method for compressing molding material by means of punches and dies, comprising;

using solid dispersion powdered or granulated as said molding material,
housing said punches and said dies in a spraying chamber,
applying the lubricant on the surfaces of said punches and said dies while the lubricant sprayed in said spraying chamber is mixed with positive pulsating vibration air, and
tabletting said molding material by means of said punches applied with said lubricant on the surface thereof and said dies applied with said lubricant on the surface thereof.

5. The tablet production method as set forth in any one of clams 1 - 4, wherein spraying amount of lubricant per tablet in said sampling chamber is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent.

6. The tablet production method as set forth in any one of clams 1 - 5, wherein said punches are provided with a projected line for forming a dividing line of a tablet.

7. The tablet production method as set forth in claim 1 or 2 wherein following steps are continuously executed;

housing said punches and said dies in said sampling chamber,
generating pulsating vibration air, spraying lubricant mixed in air in said spraying chamber, and applying the lubricant on the surfaces of said punches and said dies while the lubricant sprayed in said spraying chamber is mixed with said pulsating vibration air, and
tabletting said molding material by means of said punches applied with said lubricant on the surface thereof and said dies applied with said lubricant on the surface thereof.

8. The tablet production method as set forth in claim 3 or 4, wherein following steps are continuously executed;

housing said punches and said dies in said sampling chamber,
applying the lubricant on the surfaces of said punches and said dies while the lubricant sprayed in said spraying chamber is mixed with said positive pulsating vibration air, and
tabletting said molding material by means of said punches applied with said lubricant on the surface thereof and said dies applied with said lubricant on the surface thereof.

9. The tablet production method as set forth in any one of clams 1 - 8, wherein tabletting pressure for said molding compound by means of said punches applied with said lubricant on the surface thereof and said dies applied with said lubricant on the surface thereof is low.

10. A tablet including;

granule containing active agent in diluting agent, and
lubricant only on a surface of the tablet,
said granule being compound powdered or granulated which is denaturalized or inactivated when tabletted at high pressure.

11. A tablet including ;

granule containing active agent in diluting agent, and
lubricant only on a surface of the tablet,
said granule being solid dispersion powdered or granulated.

12. The tablet as set forth in claim 10 or 11 wherein lubricant amount per tablet is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent.

13. The tablet as set forth in any one of clams 10 - 12, wherein the shape of the tablet is anomalous.

14. The tablet as set forth in any one of clams 10 - 13, wherein the tablet has a dividing line on the surface thereof.

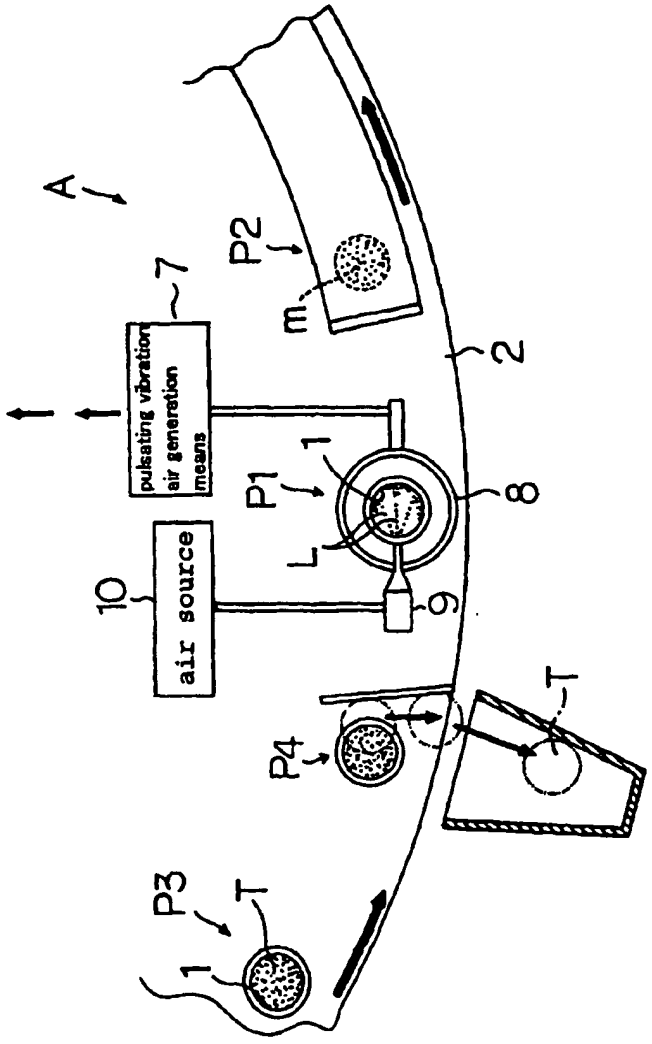

A
P2
m
7
pulsating vibration air generation means
2
P1
1
8
L
10
air source
9
T
P4
P3
T
1

Fig.1

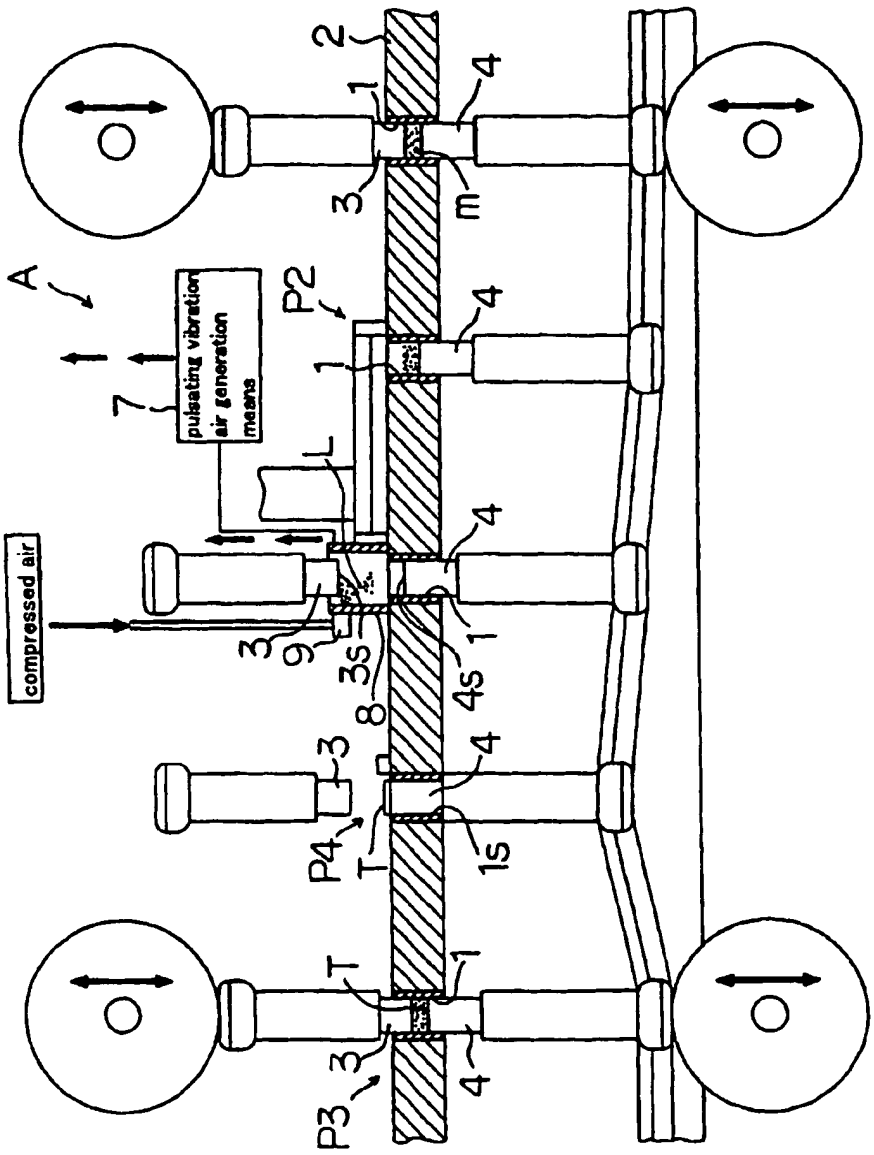

A
pulsating vibration air generation means
compressed air
P2
P4
P3
T
L
m
1s
3s
4s

Fig.2

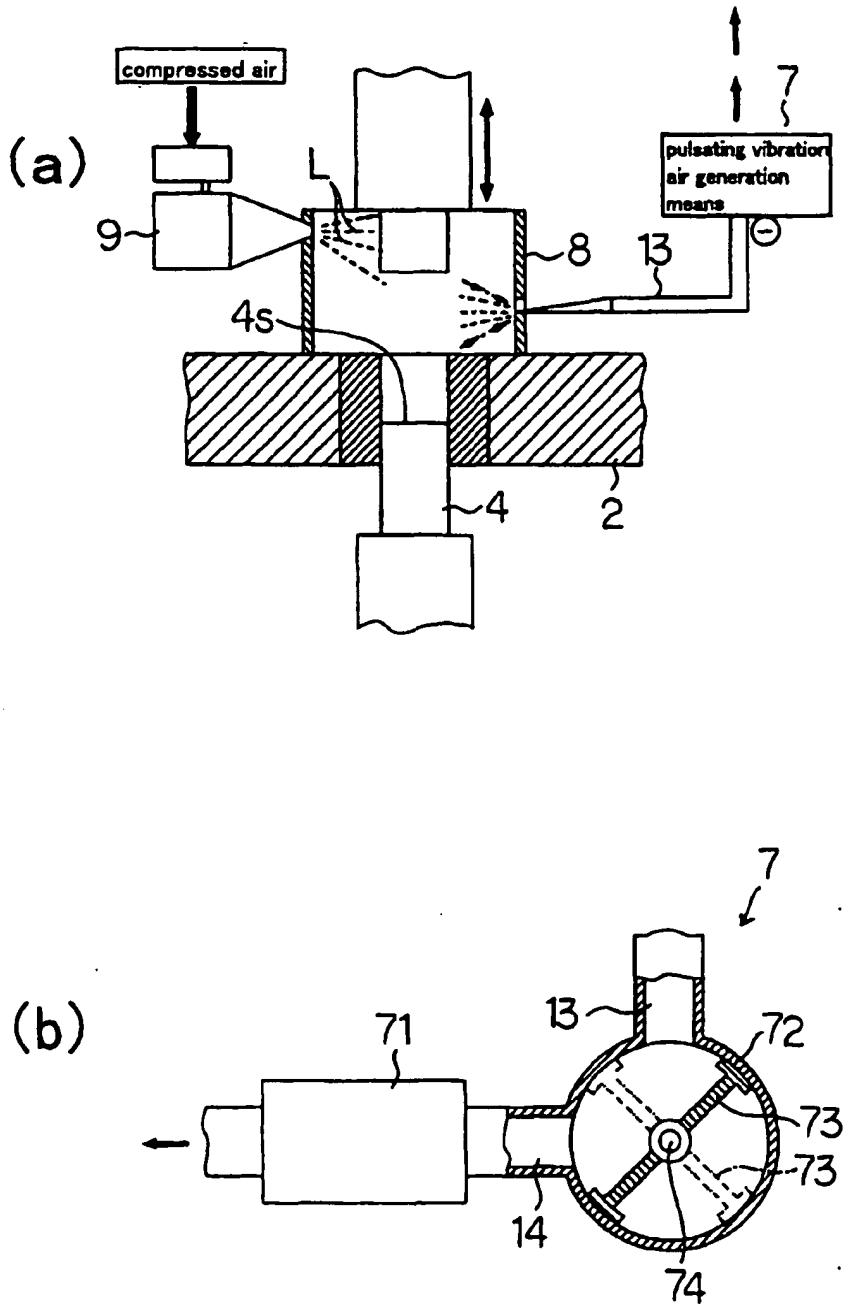
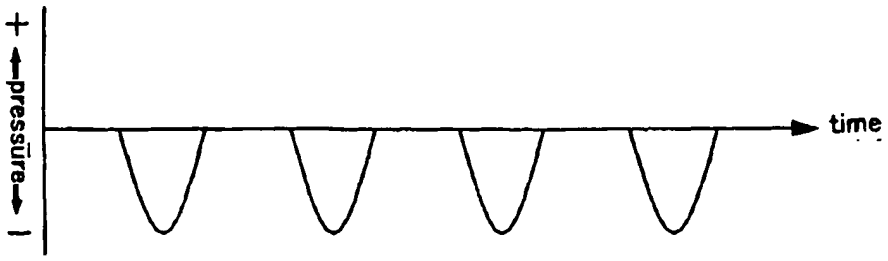


Fig.3

(a)



(b)

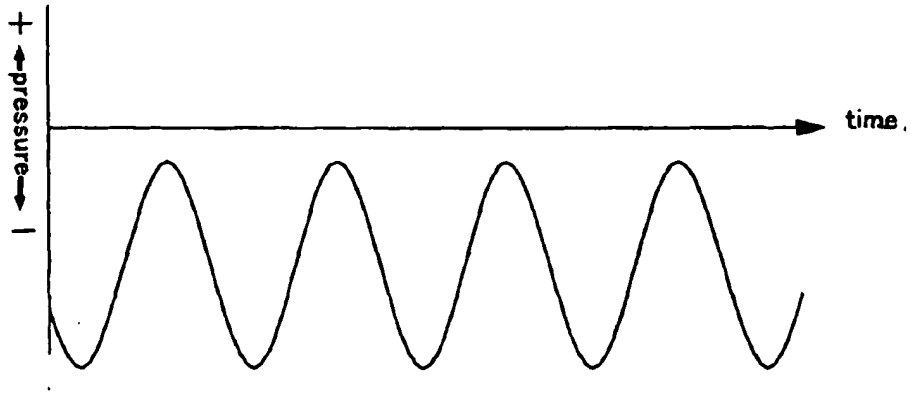


Fig.4

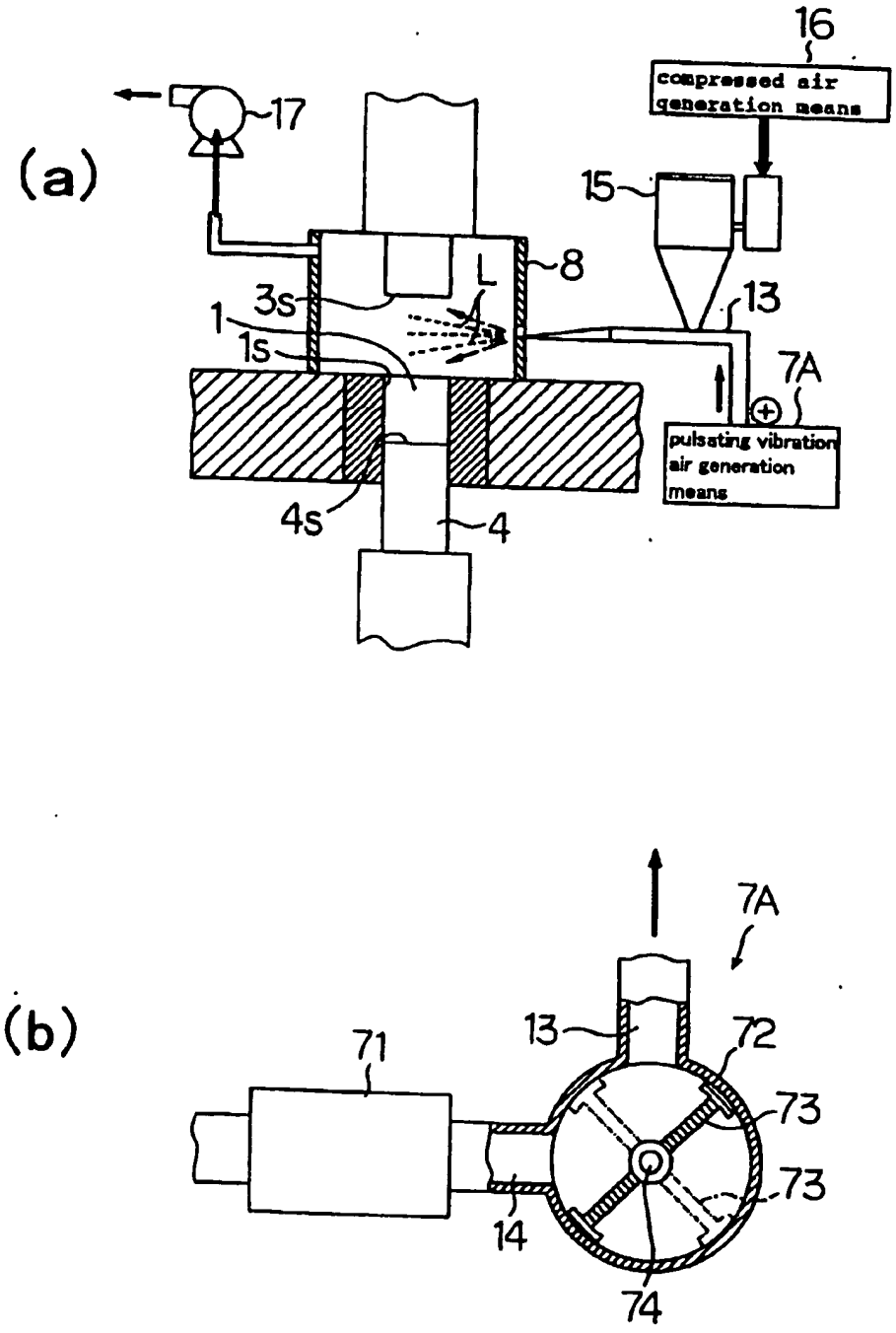
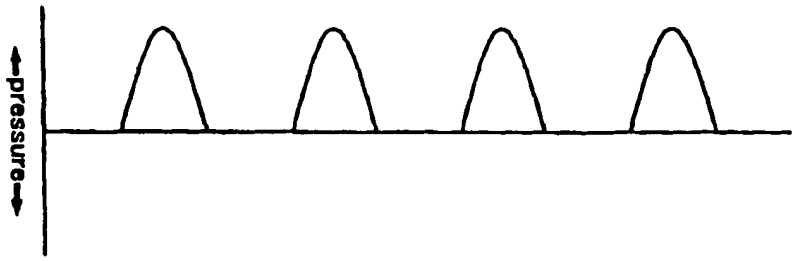

(a)
16
compressed air generation means
17
15
8
L
3s
1
1s
13
7A
pulsating vibration air generation means
4s
4
(b)
7A
13
72
71
73
73
14
74

Fig.5

(a)



(b)

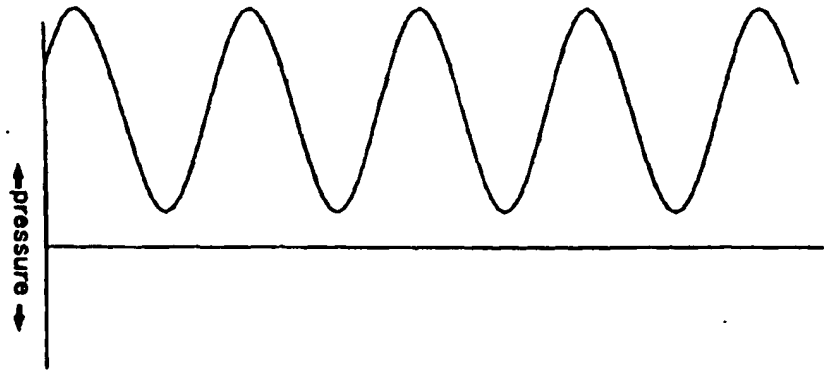


Fig.6

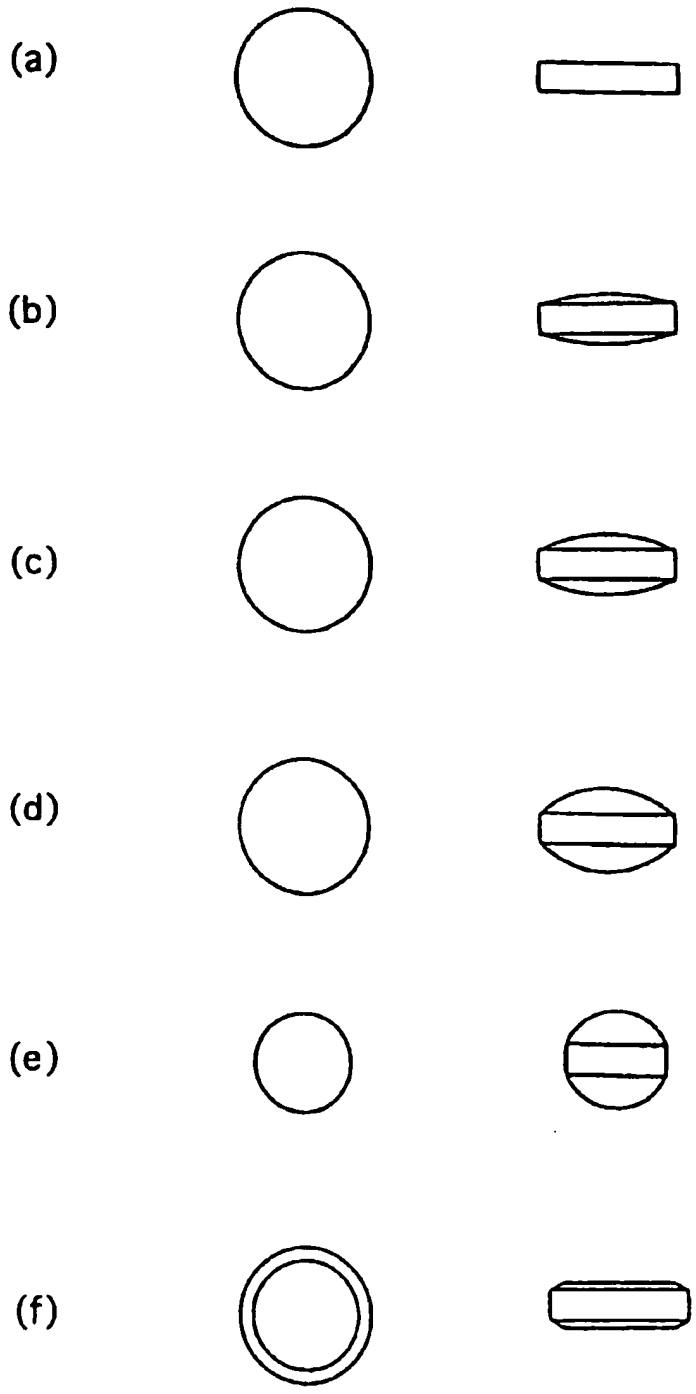


Fig.7

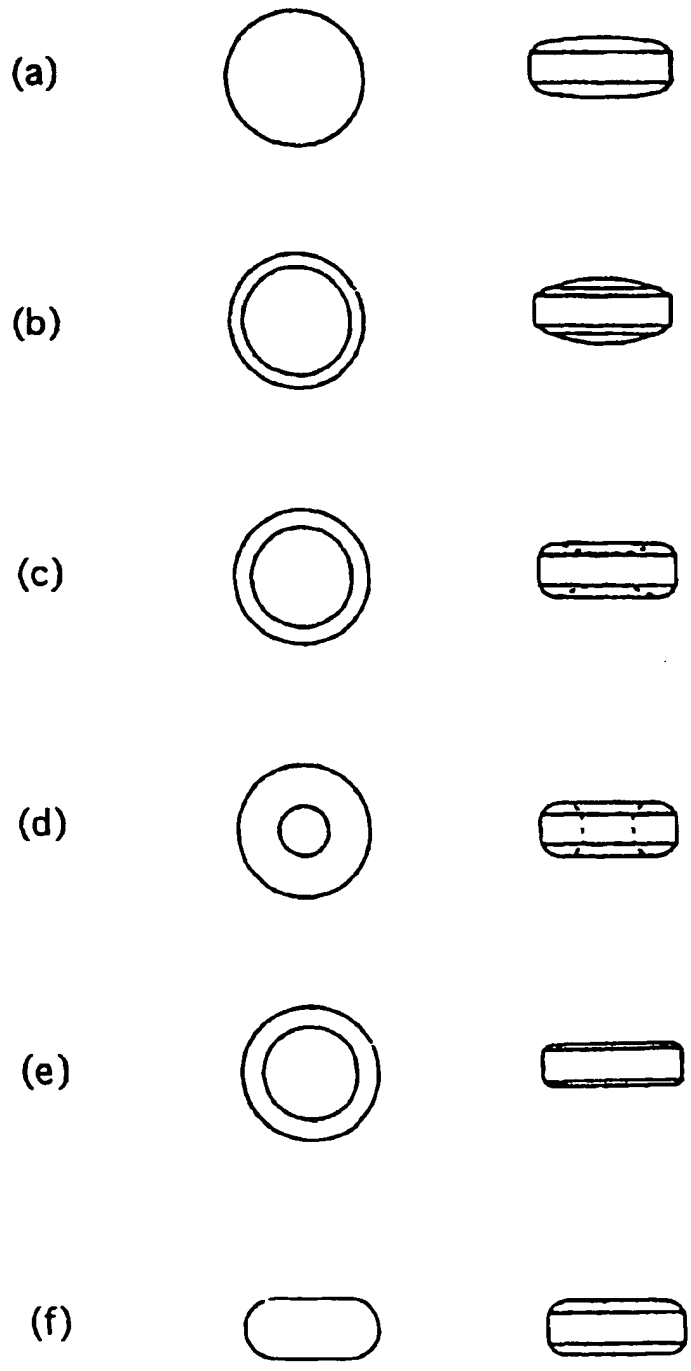


Fig.8

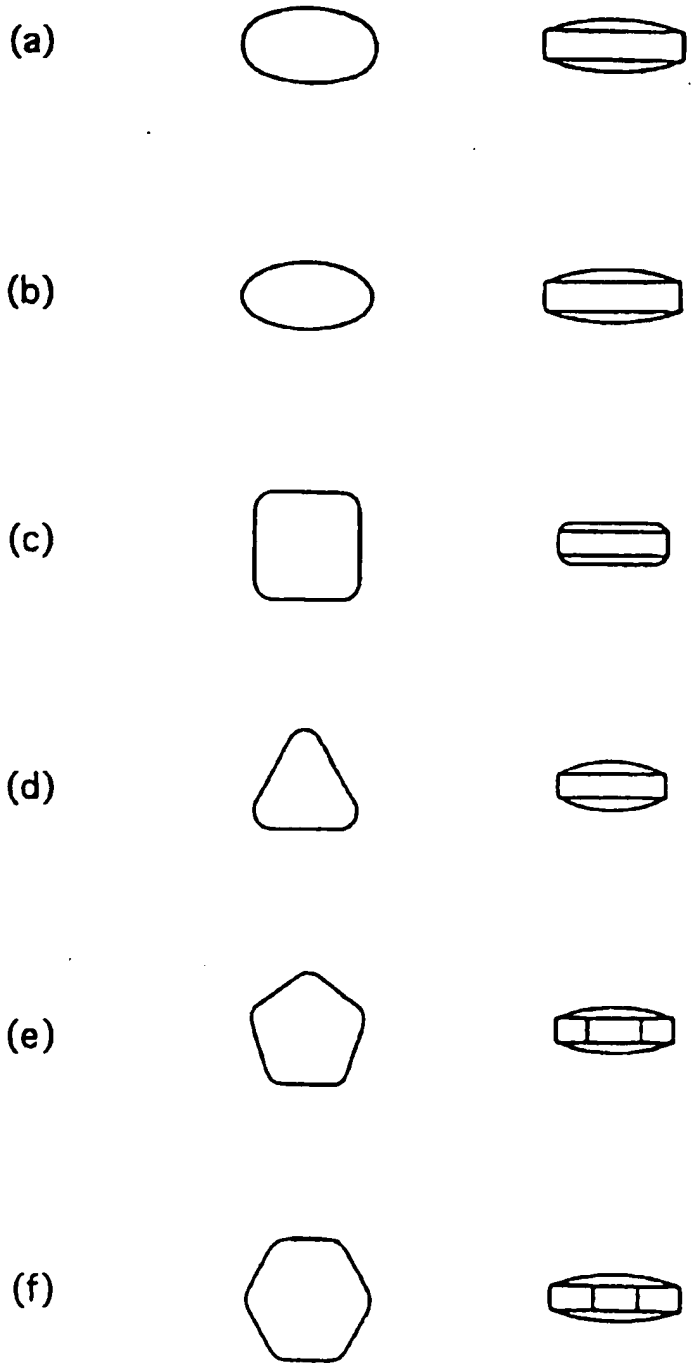


Fig.9

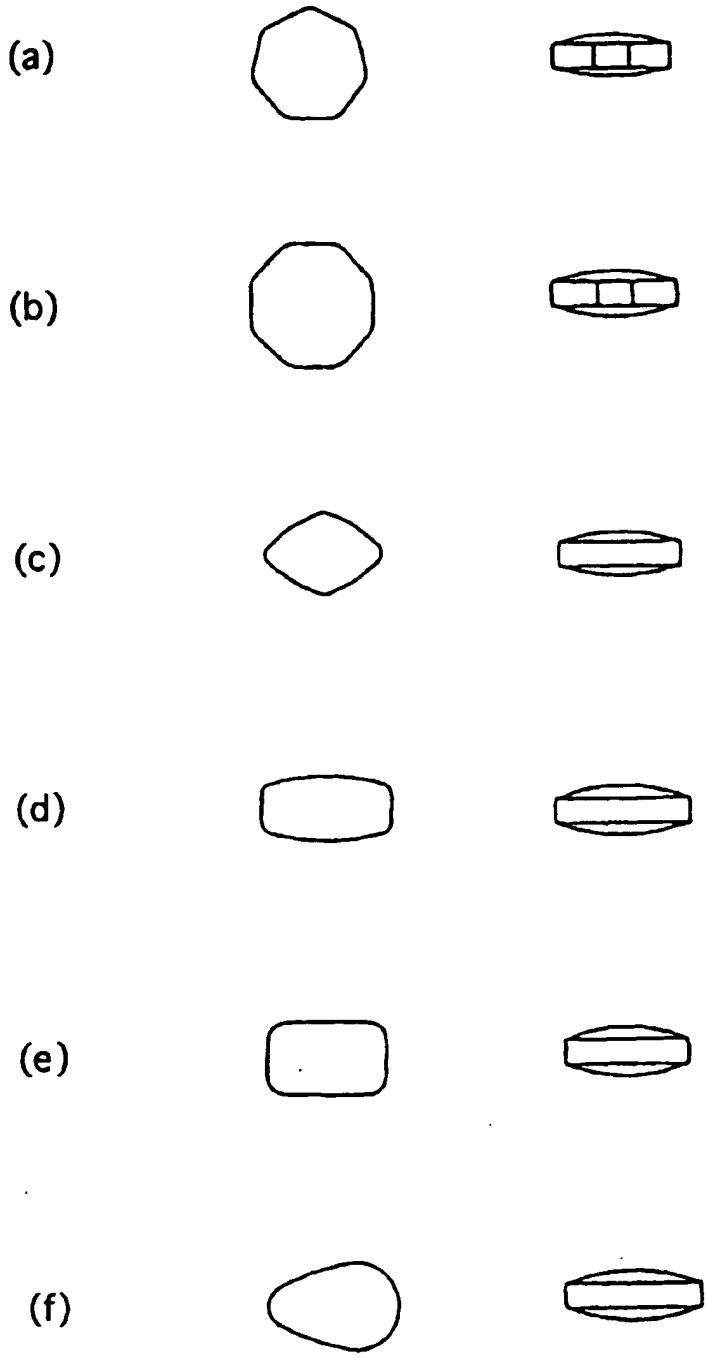


Fig.10

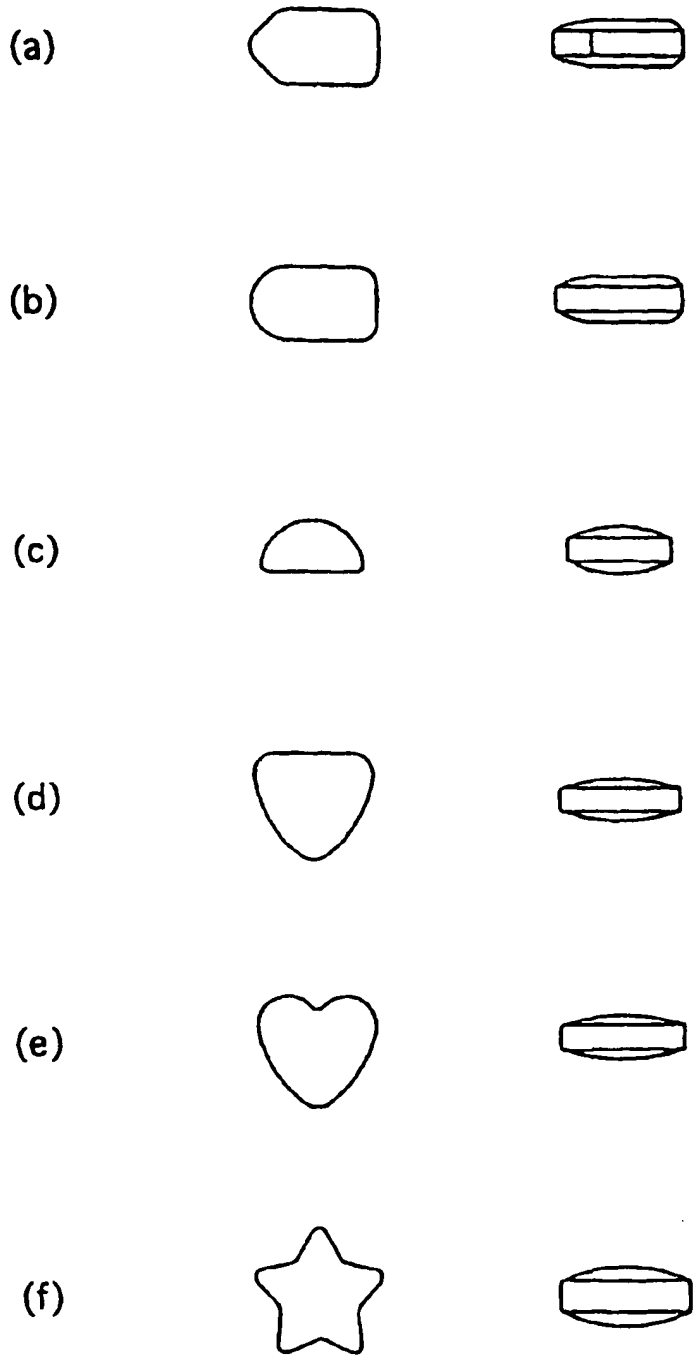


Fig.11

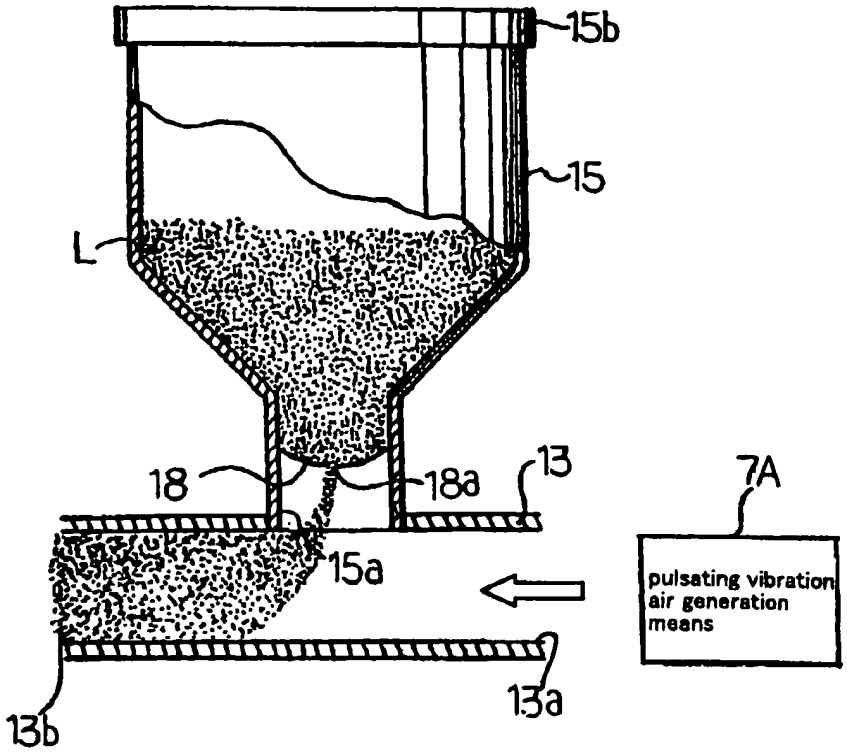

15b
15
L
18
18a
13
7A
15a
pulsating vibration air generation means
13a
13b

Fig.12

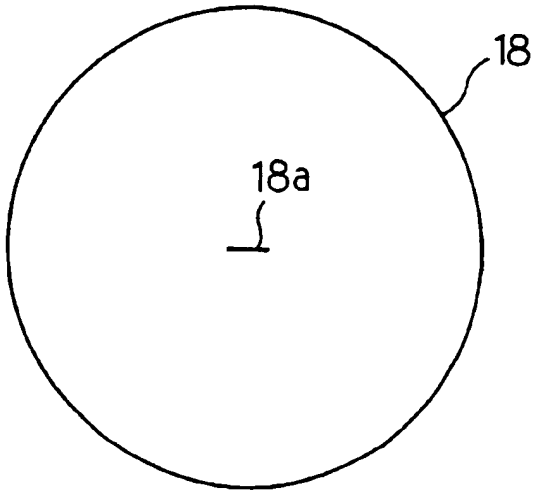


Fig.13

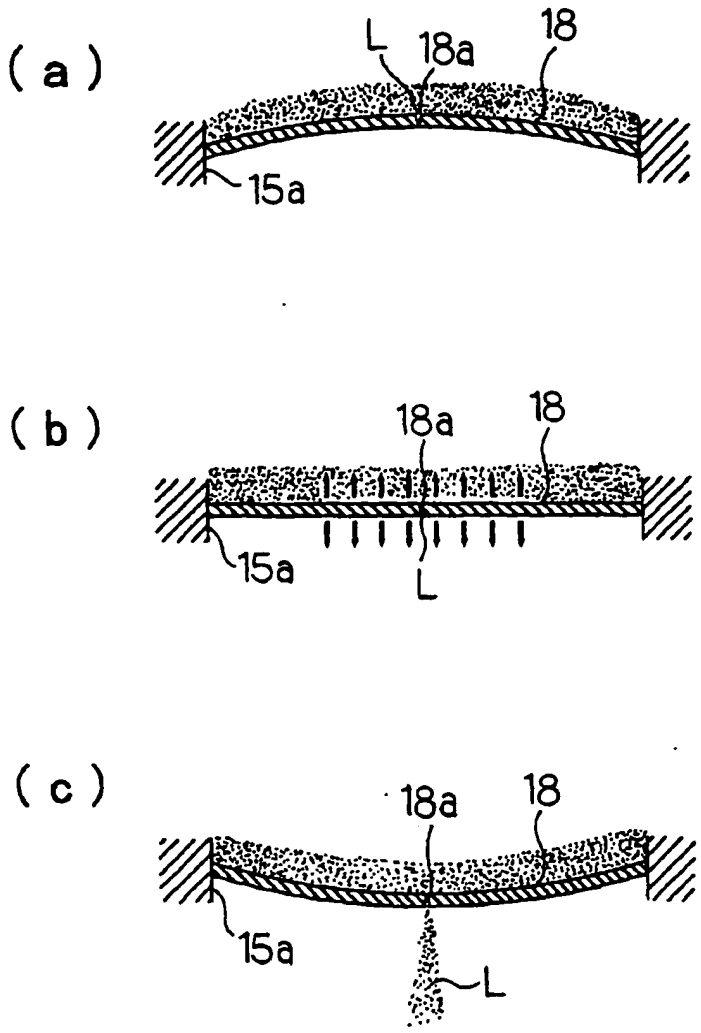


Fig.14

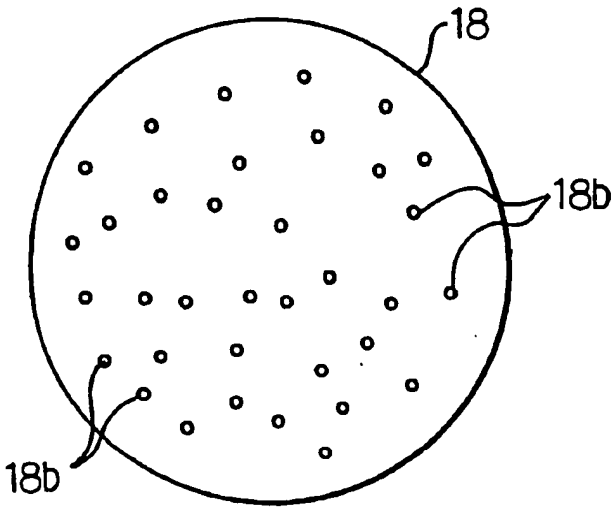


Fig.15

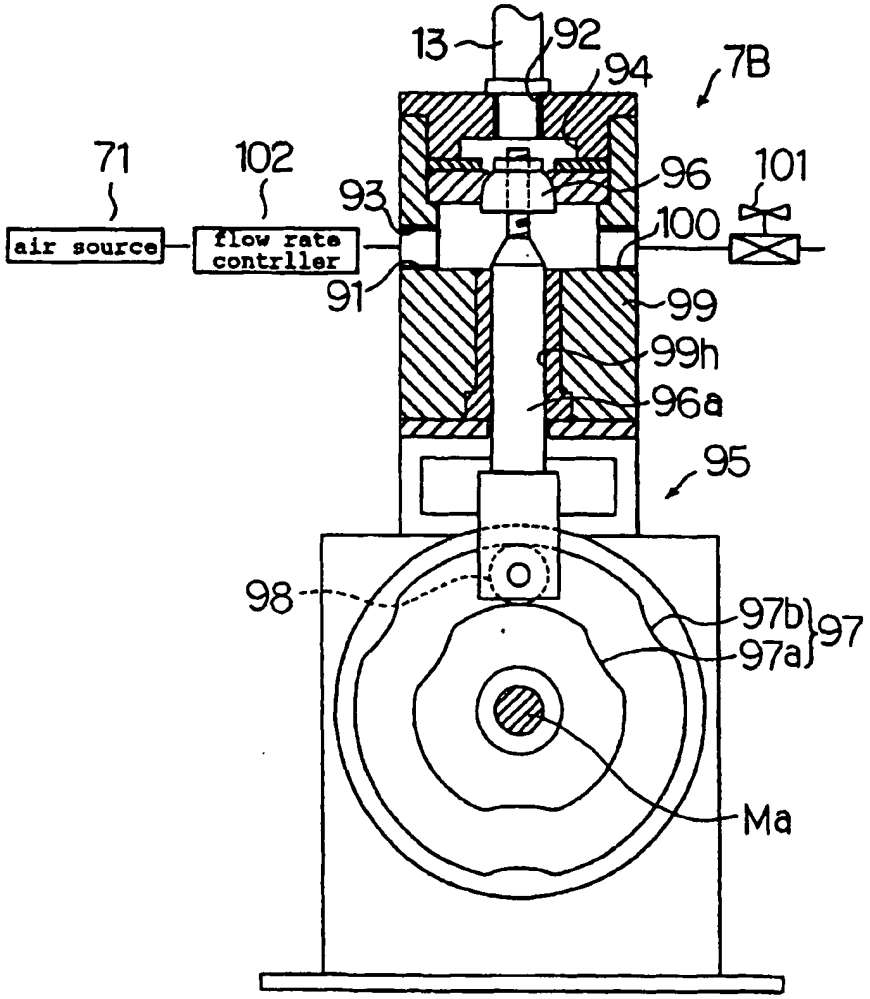

13
92
94
7B
71
102
93
96
101
air source
flow rate controller
100
91
99
99h
96a
95
98
97b
97
97a
Ma

Fig.16

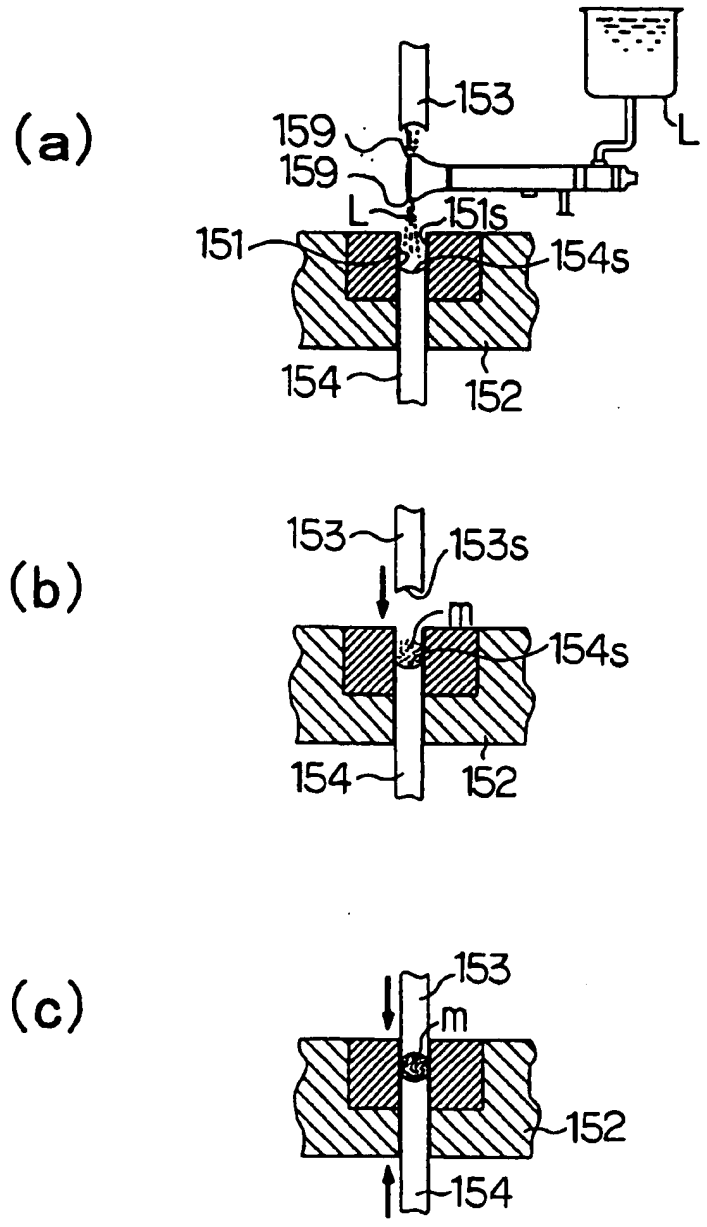


Fig.17

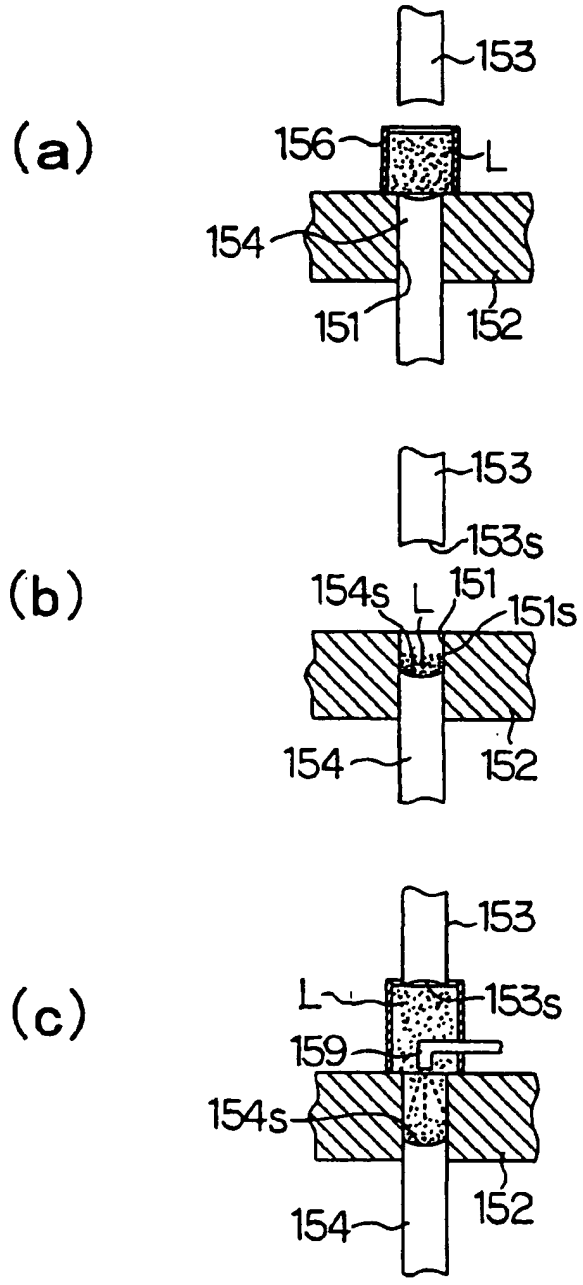


Fig.18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/01861

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] A61J3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] A61J3/10, B30B11/00, 11/08, A61K9/00-9/72, 47/00-47/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Toroku Jitsuyo Shinan Koho 1994-1999
Kokai Jitsuyo Shinan Koho 1971-1999 Jitsuyo Shinan Toroku Koho 1996-1999

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 45-22959, B1 (Carter Wallace Inc.), 3 August, 1970 (03. 08. 70), Column 1, line 26 to column 2, line 6 (Family: none)	1, 3, 5-10 12-14
Y	JP, 7-124231, A (Kyowa Hakko Kogyo Co., Ltd.), 16 May, 1995 (16. 05. 95), Full text ; all drawings & EP, 650826, A1 & US, 5700492, A	1-14
Y	JP, 2-206, A (Fujisawa Pharmaceutical Co., Ltd.), 5 January, 1990 (05. 01. 90), Full text & EP, 315964, A & US, 5093372, A	2, 4-9, 11-14
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☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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8 July, 1999 (08. 07. 99)	21 July, 1999 (21. 07. 99)
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/01861

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 8-277218, A (Kyowa Hakko Kogyo Co., Ltd.), 22 October, 1996 (22. 10. 96), Claims 1, 3 ; Figs. 1, 2 (Family: none)	6, 13, 14

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(54) TABLET MANUFACTURING METHODS AND TABLET

(57) A production method a tablet including at least active substance by means of a die and a pair of punches, comprising steps of; preparing molding material including active substance; housing said die and said pair of punches in a spraying chamber; generating pulsating vibration air and spraying lubricant mixed in air in said spraying chamber; applying lubricant on the surfaces of said die and said pair of punches housed in said spraying chamber while the lubricant sprayed in said spraying chamber is mixed with said pulsating vibration air; and tabletting said molding material by means of said die and said pair of punches on which surfaces said lubricant is applied.

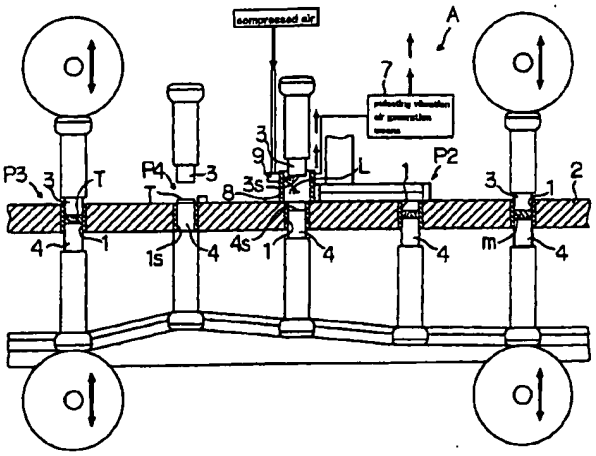


Fig.2

EP 1 070 497 A1

Description

Technical Field

[0001] The present invention relates to a tablet production method, particularly a method wherein a tablet can be immediately disintegrated at an objective part, a method wherein a tablet with an engraved mark or a dividing line or an anomalous tablet can be produced without causing sticking and so on, and a method wherein a tablet including granule covered with film (so called multiple unit tablet) can be easily manufactured without damaging function of the granule.

[0002] The present invention also relates to a tablet which can be rapidly disintegrated at a target region of a living body such as oral cavity, a tablet wherein function of the contained granule isn't damaged, and a tablet added with function such as sustained release which isn't damaged when divided.

Background Art

[0003] A tablet and a capsule are very useful pharmaceuticals for carrying and dosing and a tablet is easy to be taken for elder person or a patient because it doesn't float on the water when dosing with water. Further, it has many advantages such that production cost can be held down. Therefore, it is a most multipurpose dosage form for oral administration and intrabuccal administration.

[0004] In these years, a tablet which is formed anomalous other than circular in order to distinguish the product at a glance, a tablet provided with an engraved mark such as a company name or a chemical code, and a tablet with a dividing line which can be divided along the dividing line in order to administer most suitable amount of drug depending on the age and weight of a patient have been rapidly come into wide use.

[0005] There are several kinds of tablets such as an uncoated tablets made by compressing powder or granule, a coating tablet covered with a film on the tablet body for the purpose of prolongation, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste, and so on, a matrix type tablet (single unit tablet) tabletted by dispersing active substance in a base matrix of release inhibition material with hydrophobic property or hydrophilic property, and a tablet (multiple unit tablet) 101 including granule produced by tabletting molding material in which granule 102 containing active substance, diluting agent 103, and lubricant 104 are uniformly mixed liken in Fig.20(a).

[0006] As granule 102 containing active substance included in the tablet (multiple unit tablet) 101, in order that a fixed amount of active substance is continuously released for a fixed time by one dosage of the tablet 101 or the granule 102 is dissolved at an objective region such as intestine, there are granule of which part 102a containing active substance is covered with a film 102b having sustained release or high solubility in intestine as shown in Fig.20(b) or granule wherein the active substance 102c is dispersed in a base insoluble in water such as fat, wax, and Vaseline or in the base matrix 102d of hydrophobic high molecular material such as silicon rubber, and plastic and an interface of the base matrix 102d is retreated accompanied with release of the active substance 102c from the base matrix 102d so that the active substance 102c is continuously leased as shown in Fig.20(c).

[0007] Conventionally such a tablet with an engraved mark or a dividing line, an anomalous tablet, and a tablet including granule (multiple unit tablet) has been manufactured by an internal lubricant method and an external lubricant spraying method.

[0008] According to an internal lubricant method, lubricant such as magnesium stearate, lauryl sodium sulphate, and talc are mixed in a molding material other than active substance and diluting agent in order to execute smooth tabletting by preventing adhering of molding material on punches and dies and griding between the punches and the dies at the time of producing tablets by compressing molding material by means of the punches and the dies, and for the purpose of preventing defective tablets causing sticking (phenomenon causing hurt on a tablet surface when molding material is adhered on the punch surface), capping (phenomenon showing peeling of the top of tablet like a cap), laminating (phenomenon showing peeling of the tablet like a layer), and binding (phenomenon causing lengthwise hurt on the tablet surface when a tablet is discharged from the die).

[0009] As an external tablet spraying method, a production method has been already supposed in JP-B-41-11273 and JP-A-56-14098.

[0010] Fig.21 shows a production method disclosed in JP-B-41-11273.

[0011] According to the method comprised of charging a fixed amount of material to be tabletted in a die, tabletting the charged material in the die by means of a pair of an upper and a lower punches, and discharging the tablet, as a procedure before molding material is charged in the die 151 as shown in Fig.21(a), a spray nozzle 159 for spraying lubricant L is provided above the die 151 and lubricant L is applied on a surface 153s (lower surface) of the upper punch 153 and a surface 154s (upper surface) of the lower punch 154, both of which are provided for the die 151 which comes to a place where the spray nozzle 159 is placed. Then molding material is charged in the die 151 as shown in Fig.21(b), and the charged material m is compressed by means of the upper punch 153 on which lower surface 153s is applied

with lubricant L and the lower punch 154 of which upper surface 154s is applied with lubricant as shown in Fig.21(c).

[0012] The member indicated by the numeral 152 in Fig.21 shows a rotary table provided with the die 151 (The same numeral is used in Fig.22.).

[0013] Fig.22 shows a tablet production method described in JP-A-56-14098.

[0014] According to this method, before molding material is charged in a die 151, a spray 156 for spraying lubricant L and a nozzle 159 for spraying air are provided above the die 151. Lubricant L is sprayed in the spray 156 when the die 151 comes where the spray 156 is provided as shown in Fig.22(a), lubricant is applied on a surface 154s (upper surface) of a lower punch 154 provided for the die 151 as shown in Fig.22(b). As shown in Fig.22(c), compressed air is sprayed on the lower punch 154 at a position where the nozzle 159 is provided, lubricant L applied on the upper surface 154s of the lower punch 154 is blown upwardly to be dispersed, then the dispersed lubricant L is attached on an inner wall 151s of the die 151 and a surface 153s (lower surface) of an upper punch 153. Thereafter, molding material m is compressed to produce a tablet by means of lubricated inner wall 151s of the die 151, lubricated lower surface 153s of the upper punch 153, and lubricated upper surface 154s of the lower punch 154.

[0015] However, a tablet produced by an internal lubricant method includes lubricant therein and has a problem wherein disintegrating time of a tablet is delayed because of water repellency of lubricant so that it becomes hard to produce a tablet which is required to be rapidly disintegrated at a target region like an intrabuccally rapidly disintegrable tablet.

[0016] Moreover, when a tablet with an engraved mark, a tablet with a dividing line or an anomalous tablet with different shape are produced according to prior internal lubricant method or external lubricant spraying method, the produced tablet is apt to cause sticking, capping, laminating and binding.

[0017] According to an internal lubricant method, high tabletting pressure is required (generally 1 ton/cm^2 - 2 ton/cm^2) in order to obtain practical hardness. Therefore, when a tablet containing granule (multiple unit tablet) 101 is produced according to this method, the film 102b formed on the surface of the granule 102 contained in the tablet 101 is damaged when tabletted, or the granule 102 is plastically deformed or destroyed when unreasonable force is applied to the granule 102 so that functions of the granule 102 contained in the tablet 101 such as rapid release, sustained release, prolongation of mode of action, or function of dissolving at an objective region can't be obtained.

[0018] Conventionally as a method to prevent the film 102b formed on the surface of the granule 102 from being damaged while tabletting, there has been disclosed multiple granule in JP-A-62-103012, a chewable drug tablet containing gustation shielding agent in JP-A-2-106, and a rapid release microcapsule in JP-A-57-150612. However, they are produced by pharmaceutically devising the construction and material of the film 102b. According to such a method, material and construction to be selected are limited and a film usually used for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, and prevention of bitter taste can't be used.

[0019] Further, as a method to keep the function of the film by restraining breakage of the film of granule, there is a method wherein practical hardness of a tablet is obtained by tabletting while dispersing granule in a large amount of diluting agent. According to such a method, there is a problem that a tablet containing a large amount of granule therein can't be produced.

[0020] From the above-mentioned problems, application of a tablet containing granule (multiple unit tablet) is limited and pharmaceuticals containing granule, so called microcapsule are not launched on the marked as a formulation such as tablet which is easily taken by a patient or patients but as formulations such as capsule or granule which are not easily taken by a patient or patients.

[0021] A single unit type tablet which is coated with such as film or sugar on the surface of the tabletted uncoated tablet is popular as a tablet having the functions such as prolongation of made of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine or prevention of bitter taste. However, in case that such a single unit type tablet is formed as a dividable tablet having a dividing line on the surface, the film is destroyed and the function added to the tablet is lost when the tablet is divided. Therefore, it can't meet the requirement of physician or pharmacist of a hospital or a clinic to launch on the market a dividable tablet with prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine or prevention of bitter taste which can minutely prepare an appropriate amount in conformity to each patient.

[0022] The present invention is proposed to solve the above-mentioned problems. The first object of the present invention is to provide a production method of a tablet which is required to be immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet.

[0023] The second object of the present invention is to provide a production method of a tablet with an engraved mark or a dividing line or an anomalous tablet without causing sticking, capping, laminating and binding.

[0024] The third object of the present invention is to provide a tablet production method wherein a tablet containing granule (multiple unit tablet) can be produced without damaging the function of the granule (which may be called as a microcapsule) contained therein, to provide a tablet containing granule (multiple unit tablet) which can be immediately dissolved at an objective region, a tablet containing granule (multiple unit tablet) of which function isn't damaged without

specially devising the construction and the material of the film formed on the granule. Moreover, the object of the present invention is to provide a dividable tablet with a dividing line which has prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste, and such functions aren't damaged when the tablet is divided.

Disclosure of the Invention

[0025] The inventors of the present invention have done research on a tablet production method for a long time and found by experiments that when punches and a die of a tabletting machine are housed in a spraying chamber, pulsating vibration air is generated in the spraying chamber, lubricant is applied on the surfaces of the punches and the die, and molding material is tabletted by means of the lubricated punches and die to produce a tablet with an engraved mark or a dividing line or an anomalous tablet, such tablets haven't caused sticking, capping, laminating and binding. After hard endeavor, they have completed the present invention.

[0026] Further the inventors have already proposed a tablet production method in JP-A-7-124231 wherein molding material is prevented from adhering on the punches and the dies so that molding material can be continuously tabletted smoothly and stably for a long time and moreover a tablet can be produced without adhering molding material on the punches and the dies even if the amount of used lubricant is remarkably reduced. The inventors have thought that when this method is used, a tablet which has enough practical hardness and further its disintegrant time isn't delayed can be produced even if tabletting pressure is low. After hard endeavor, they have completed the present invention.

[0027] According to the tablet production method as set forth in claim 1, a tablet including at least active substance is produced by means of a die and a pair of punches. The method is comprised of preparing molding material including active substance; housing the pair of punches and the die in a spraying chamber; generating pulsating vibration air and spraying lubricant mixed in air in the spraying chamber; applying lubricant on the surfaces of the pair of punches and the die housed in the spraying chamber while the lubricant sprayed in the spraying chamber is mixed with the pulsating vibration air, and tabletting the molding material by means of the pair of punches and the die on which surfaces the lubricant is applied.

[0028] Several kinds of lubricant can be used for the tablet production method of the present invention. Lubricant isn't specifically limited, for example, there are stearate acid metal salt (magnesium stearate, calcium stearate and so on), stearic acid, sodium lauryl sulfate, sodium lauryl magnesium, powdered gum arabic, carnauba wax, anhydrous silicic acid, magnesium oxide, silic acid hydrate, boric acid, fatty acid sodium salt, leucine, and so on which have been commonly used. One of them may be used solely or more than two of them may be combined.

[0029] According to the tablet production method of the present invention, diluting agent is added in molding material for forming the shape of a tablet other than active substance.

[0030] As for diluting agent, there are several kinds, such as saccharides (lactose, sucrose, glucose, mannitol, and so on), starch (for example, potato, wheat, corn and so on), inorganic substance (calcium carbonate, calcium sulfate, sodium bicarbonate, sodium chloride, and so on), crystalline cellulose, powdered plant (powdered glycyrrhiza, powdered gentian, and so on).

[0031] Molding material containing active substance may include binder, supplement such as solution adjuvant, solubilizer, or disintegrant, corrigent, colorant, adjuvant for pharmaceiticals, antioxidant, preservative, opacifying agent, antistatic agent, aroma, sweetening agent, fluidizing agent, flavoring agent, and so on if required other than active substance and diluting agent. However, molding material is powdered or granular material which doesn't include lubricant.

[0032] "Pulsating vibration air" in the present invention means a wave of air of which air pressure is changed. Positive or negative pulsating vibration air may be used and of which amplitude, wave length, wave shape, frequency, and period may not be limited if it can generate air vibration all over the spraying chamber and forcibly diffuse the particle of lubricant sprayed therein.

[0033] "Positive pulsating vibration air" used in this invention includes both positive pulsating vibration air of which peak and valley are positive and positive pulsating vibration air of which peak is higher than atmospheric pressure and valley is almost the same as atmospheric pressure.

[0034] "Negative pulsating vibration air" used in this invention includes both pulsating vibration air of which peak and valley are negative and pulsating vibration air of which peak is almost the same as atmospheric pressure and valley is negative.

[0035] Conditions of pulsating vibration air depend on size and shape of punches and dies of a tabletting machine, size and shape of a spraying chamber, how a lubricant spraying means is provided, and description of active substance. Therefore, conditions can't be simply defined, however it is easily defined based on experiments.

[0036] According to this tablet production method, pulsating vibration air is generated and lubricant is sprayed in the spraying chamber. As a result, the sprayed lubricant is mixed with pulsating vibration air.

[0037] Further according to this method, lubricant is applied on the surfaces of the die and the pair of punches under a Condition wherein lubricant is mixed with pulsating vibration air, namely a condition wherein lubricant is hardly

attached on the surfaces of the punches and the die.

[0038] When lubricant is designed to be applied on the surfaces of the punches and the die under such a hard condition, lubricant can be uniformly applied thereon. This fact has been confirmed by an experiment by the present inventors.

[0039] Consequently, molding material is prevented from adhering on the pair of punches and the die while tabletted so that sticking is hardly caused.

[0040] Moreover, as the result that lubricant is uniformly applied on the surface of the pair of punches and the die, the produced tablet doesn't cause sticking even if the amount of used lubricant per a tablet is remarkably reduced comparing with the prior internal lubricant method and the prior external lubricant spraying method.

[0041] Therefore, a tablet of which surface a minute amount of lubricant is attached can be produced. Such a tablet doesn't happen that disintegrant time doesn't delay because of water repellency of lubricant.

[0042] According to the production method, a tablet which can be rapidly disintegrated at an object region such as target region of living body can be produced.

[0043] Further according to the production method, because lubricant isn't included in molding material, a tablet with practical hardness can be produced even if tabletting pressure is lower than that of prior art when molding material is tabletted by means of a pair of punches and a die.

[0044] Hence, when a tablet including granule having film on the surface is produced, the film isn't destroyed.

[0045] Also when a tablet including granule containing active substance in a base matrix is produced, the function of the contained matrix isn't damaged.

[0046] According to the tablet production method as set forth in claim 2, a tablet including at least active substance is produced by means of a die and a pair of punches. The method is comprised of the steps of; preparing molding material including active substance; housing the pair of punches and the dies in a spraying chamber; spraying lubricant mixed in pulsating vibration air in the spraying chamber; applying lubricant on the surfaces of the pair of punches and the die housed in the spraying chamber; and tabletting the molding material by means of the pair of punches and the die on which surfaces the lubricant is applied.

[0047] According to this tablet production method, lubricant mixed with pulsating vibration air is designed to be sprayed in the spraying chamber.

[0048] Further according to this method, lubricant is applied on the surfaces of the die and the pair of punches under a condition wherein lubricant is mixed with pulsating vibration air, namely a condition wherein lubricant is hardly attached on the surfaces of the punches and the die.

[0049] When lubricant is designed to be applied on the surfaces of the punches and the die under such a hard condition, lubricant can be uniformly applied thereon.

[0050] Consequently, molding material is prevented from adhering on the pair of punches and the die while tabletted so that sticking is hardly caused.

[0051] Moreover, as the result that lubricant is uniformly applied on the surfaces of the pair of punches and the die, the produced tablet doesn't cause sticking even if the amount of used lubricant per a tablet is remarkably reduced comparing with the prior internal lubricant method and the prior external lubricant spraying method.

[0052] Therefore, a tablet of which surface a minute amount of lubricant is attached can be produced. Such a tablet doesn't happen that disintegrant time delays because of water repellency of lubricant.

[0053] According to the production method, a tablet which can be rapidly disintegrated at an object region such as target region of living body can be produced.

[0054] Further according to the production method, because lubricant isn't included in molding material, a tablet with practical hardness can be produced even if tabletting pressure is lower than that of prior art when molding material is tabletted by means of a pair of punches and a die.

[0055] Hence, when a tablet including filmed granule on the surface is produced, the film isn't destroyed.

[0056] Also when a tablet including granule containing active substance in a base matrix is produced, the function of the contained matrix isn't damaged.

[0057] The tablet production method as set forth in claim 3 is characterized in that pulsating vibration air used in the method of claim 2 is positive pulsating vibration air.

[0058] According to this method, a spraying means for spraying lubricant mixed with positive pulsating vibration air is required to be provided so that the system can be simplified.

[0059] Further the inventors have paid attention in JP-A-7-124231 that when material is tabletted at a remarkably low pressure, the produced tablet has enough practical hardness. They have thought that a tablet including granule can be produced by this method without damaging the coated film of the granule, so called microcapsule, damaging the contained granule, nor deforming plasticity. After hard endeavor, they have completed the present invention.

[0060] According to the tablet production method as set forth in claim 4, a tablet including granule containing at least active substance is produced by means of a die and a pair of punches. The method is comprised of the steps of; mixing granule containing active substance and diluting agent uniformly and preparing molding material including gran-

ule containing active substance; housing the pair of punches and the dies in a spraying chamber; generating pulsating vibration air and spraying lubricant mixed in air in the spraying chamber; applying lubricant on the surfaces of the pair of punches and the dies housed in the spraying chamber while the lubricant sprayed in the spraying chamber is mixed with the pulsating vibration air; and tabletting the molding material including granule containing the active substance by means of the pair of punches and the die on which surfaces the lubricant is applied.

[0061] "A tablet including granule containing at least active compound" includes a tablet produced by tabletting only granule containing active substance and a tablet produced by tabletting molding material in which granule containing at least active substance, diluent, bulking agent, filler, and other diluting agent such as excipient are uniformly mixed. Further molding material may include supplement such as solution adjuvant, solubilizer, and disintegrant, antioxidant, preservative, opacifying agent, antistatic agent, aroma, sweetening agent, fluidizing agent, flavoring agent, colorant and so on.

[0062] "Granule including active substance" includes granule which is provided with film on the part including at least active substance (therapeutic main ingredient) for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste, and granule in which active substance is dispersed in a base matrix.

[0063] Coating material for the film covering the surface of the part including active substance (therapeutic main ingredient) isn't required to be special. It may be generally used film coating agent such as sugar coating, ethylcellulose (EC), hydroxypropylsellulose (HPC), hydroxypropylmethylcellulose phthalate (HPMC), carboxymethylcellulose, and cellulose group such as hydroxypropylmethylcellulose, acetate succinate (HPMCAS), carboxymethylethylcellulose (CMEC), and cellulose acetate phthalate (CAP), acrylic acid group such as methaacrylic acid copolymer, enteric coating agent such as natural product like shellac, sustained release coating agent such as ethylcellulose (EC), sucrose ester, aminoalkylmetaacrilate copolymer, copolymer of ethylacrylate - methylmethacrylate, and several kinds of material such as coating material disclosed in JP-A-57-150612, JP-A-62-103012, and JP-A-2-106.

[0064] According to this method, a tablet with practical hardness can be produced at low tabletting pressure because lubricant isn't included in molding material. Therefore, a tablet can be produced without breaking film and granule and without causing plastic deformation even if the construction and material of the film provided for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste and the base matrix aren't devised.

[0065] The production method of a tablet including granule containing at least active substance by means of a die and a pair of punches as set forth in claim 5 is comprised of the steps of; mixing granule containing active substance and diluting agent uniformly and preparing molding material including granule containing active substance; housing the pair of punches and the die in a spraying chamber; spraying lubricant mixed in pulsating vibration air in the spraying chamber; applying lubricant on the surfaces of the pair of punches and the die housed in the spraying chamber; and tabletting the molding material including granule containing the active substance by means of the pair of punches and the die on which surfaces the lubricant is applied.

[0066] According to this method, a tablet with practical hardness can be produced at low tabletting pressure because lubricant isn't included in molding material. Therefore, a tablet can be produced without breaking film and granule and without causing plastic deformation even if the construction and material of the film provided for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste and the base matrix aren't devised.

[0067] The tablet production method as set forth in claim 6 is characterized in that the pulsating vibration air used in the tablet production method in claim 5 is a positive pulsating vibration air.

[0068] According to this method, a spraying means for spraying lubricant mixed with positive pulsating vibration air is required to be provided so that the system can be simplified.

[0069] The tablet production method as set forth in claim 7 proposes a preferable embodiment of granule containing active substance (so called microcapsule) to be included in molding material and defies granule containing active substance described in any one of claims 4 - 6 is granule containing active substance and diluting agent.

[0070] According to this method, granule containing active substance and diluting agent is used as granule containing active substance (so called microcapsule) so that the particle diameter and particle size of the granule containing active substance can be easily changed by the diluting agent.

[0071] Therefore, a tablet can be easily produced by controlling the diameter and the size of granule containing active substance so as to facilitate coating a film on the surface.

[0072] Further, the diameter and the size of granule containing active substance can be made so as to derive the function of granule to the full extent.

[0073] The tablet production method as set forth in claim 8 proposes another preferable embodiment of granule containing active substance (so called microcapsule) to be included in molding material and defies granule containing active substance used in the method as set forth in any one of claims 4 - 6 is granule containing active substance in base matrix.

[0074] "Granule containing active substance in base matrix" means granule wherein active substance (powder) is uniformly dispersed in a base insoluble in water such as fat, wax, and Vaseline or in a base matrix of hydrophobic high molecular material such as silicon rubber, and plastic.

[0075] According to this production method, because tablet can be produced at low tabletting pressure, a tabletting can be executed without destroying the function of base matrix even if granule contained in the tablet includes active substance in the base matrix.

[0076] The tablet production method as set forth in claim 9 proposes further preferable embodiment of granule containing active substance (so called microcapsule) to be included in molding material and defies granule containing active substance used in the method as set forth in any one of claims 4 - 8 is granule of which part containing active substance is coated with film.

[0077] According to this production method, because tablet can be produced at low tabletting pressure, a tabletting can be executed without destroying the coating film even if granule contained in the tablet is coated with a film.

[0078] A coating method such as well known fluidized bed coating may be used as a method for coating granule with a film.

[0079] According to the tablet production method as set forth in claim 10, the following steps as set forth in claim 1 or 4 are continuously executed; housing the pair of punches and the die in the spraying chamber; generating pulsating vibration air, spraying lubricant mixed in air in the spraying chamber; and applying the lubricant on the surfaces of the pair of punches and the die while the lubricant sprayed in the spraying chamber is mixed with pulsating vibration air; and tabletting the molding material by means of the pair of punches and the die on which surfaces the lubricant is applied.

[0080] According to this method, tabletting is continuously executed utilizing the fact that molding material isn't adhered on the punches and the die so that sticking isn't caused. A tablet including active substance and a tablet including granule containing active substance can be produced at industrial production base.

[0081] The tablet production method as set forth in claim 11 is characterized in that the following steps in claim 2 or 5 are continuously executed; housing the pair of punches and the die in the spraying chamber; spraying lubricant mixed in positive pulsating vibration air in the spraying chamber, and applying the lubricant on the surfaces of the pair of punches and the die; and tabletting the molding material by means of the pair of punches and the die on which surfaces the lubricant is applied.

[0082] According to this method, tabletting is continuously executed utilizing the fact that molding material isn't adhered on the punches and the die so that sticking isn't caused. A tablet including active substance and a tablet including granule containing active substance can be produced at industrial production base.

[0083] The tablet production method as set forth in claim 12 is characterized in that in the method of any one of claims 1 - 11 punches and a die construct a female mold of a tablet having an engraved mark or a dividing line and an anomalous tablet.

[0084] "Anomalous tablet" in this specification means a tablet with a shape except for round, for example, track (capsule), rugby ball, polygon such as triangle, rectangle, pentagon, and so on, diamond, almond, bombshell, half moon, heart, star, and so on.

[0085] According to this method, because lubricant is applied on the surface of the punches and the die constructing a female mold for a tablet with an engraved mark or a dividing line and for an anomalous tablet in the spraying chamber in which pulsating vibration air is generated, lubricant can be applied uniformly comparing with the prior external lubricant spraying method. As a result, molding material is hardly attached on the surface of the punches and the die while compressing a tablet with an engraved mark or a dividing line or an anomalous tablet so that sticking, capping, and laminating of such a tablet are prevented.

[0086] The tablet production method as set forth in claim 13 is characterized in that in the production method in any one of claims 1 - 12 tabletting pressure of the step for tabletting the molding material by means of the lubricated pair of punches and die is low.

[0087] "Low pressure" in this specification means that tabletting pressure is lower comparing with the prior internal lubricant method and the prior external lubricant spraying method. More concretely explained, this tablet production method can produce a tablet having enough practical level hardness even if its tabletting pressure is less than or equal to 1 ton/cm^2.

[0088] According to this tablet production method, as tabletting pressure for compressing molding material is low, tabletting can be executed without destroying a film even if granule contained in the tablet is covered with a film. Further, if granule contained in a tablet includes active substance in a base matrix, tabletting can be executed without destroying the function of the base matrix.

[0089] The tablet production method as set forth in claim 14 is characterized in that in the production method in any one of claims 1 - 13 the amount of lubricant sprayed in the spraying chamber is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

[0090] It is preferable to reduce the amount of lubricant as far as possible in order to prevent extension of disinte-

gration time of a tablet and lowering of hardness. It is preferable to set the amount of lubricant used for a tablet to be compressed is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

[0091] Depending on an experiment, it was found that a tablet didn't cause tabletting problems such as sticking and could be produced continuously even if the amount of lubricant was greater than 0.0001 weight percent and less than or equal to 0.1 weight percent per a tablet.

[0092] According to this method, lubricant is applied on the surface (inner wall) of the die, the surface (lower surface) of the upper punch, and the surface (upper surface) of the lower punch, all of which are housed in the spraying chamber, by means of pulsating vibration air. Namely lubricant is applied on the surfaces under a condition where lubricant is hardly attached on the surfaces. Therefore, a minute amount of lubricant can be applied on the surface (inner wall) of the die, the surface (lower surface) of the upper punch, and the surface (upper surface) of the lower punch. As a result, even if the amount of lubricant sprayed in the spraying chamber is only minute despite of kinds of active substance, diluting agent and lubricant, molding material can be prevented from sticking on the punches and the die of the tabletting machine. Consequently the amount of lubricant sprayed for tabletting at one time can be remarkably reduced.

[0093] In accordance with this method, the produced tablet doesn't include lubricant therein and minute amount of lubricant is attached on the surface so that disintegration time isn't delayed.

[0094] Therefore, if the tablet produced by this method is used as an uncoated, it becomes rapidly disintegrable tablet and a tablet which is required to be immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet can be easily produced. Further if a film coat which can be dissolved at an objective region is executed on the surface of a tablet, the tablet itself is immediately dissolved at a desired region when a film coat is dissolved, so that a tablet which can be dissolved at an objective region can be produced.

[0095] Further according to this method, tablet can be produced at a low tabletting pressure. When a tablet including granule containing active substance is produced, the granule is hardly damaged or plastic deformation is hardly caused when tabletting. Therefore, the function of the granule containing active substance in the tablet isn't apt to be damaged.

[0096] Therefore, according to the production method, if the produced tablet including granule containing active substance is used as an uncoated tablet, it becomes rapidly disintegrable tablet and a tablet which is required to be immediately disintegrated at an objective region and the granule containing active substance can be dissolved while showing its function like an intrabuccally rapidly disintegrable tablet can be easily produced. Further if a film coat which can be dissolved at an objective region is executed on the surface of a tablet, the tablet which is required that it is immediately dissolved at a desired region when a film coat is dissolved can be produced.

[0097] The tablet as set forth in claim 15 is provided with lubricant only on the surface of a tablet including granule containing active substance in diluting agent and the amount of lubricant is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

[0098] It is preferable to reduce the amount of lubricant as far as possible in order to prevent extension of disintegration time of a tablet and lowering of hardness. It is preferable to set the amount of lubricant used for a tablet to be compressed is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

[0099] Depending on an experiment, it was found that a tablet didn't cause tabletting problems such as sticking and could be produced continuously even if the amount of lubricant was greater than or equal to 0.0001 weight percent and less than or equal to 0.1 weight percent per a tablet.

[0100] According to the tablet, as lubricant isn't included therein and a minute amount is attached on the surface, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

[0101] Therefore, if the tablet is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and the tablet is immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet and active substance contained in the tablet is immediately released.

[0102] Moreover, if a film coat which can be dissolved at an objective region is executed on the surface of the tablet, the tablet itself can be dissolved at the objective region when the film coat is dissolved, so that active substance contained in the tablet is immediately released.

[0103] The tablet as set forth in claim 16 has lubricant only on the surface of the tablet including granule containing active substance in diluting agent.

[0104] According to the tablet, as lubricant isn't included therein and a minute amount is attached on the surface, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

[0105] Therefore, if the tablet is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and the tablet is immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet and granule containing active substance (so called microcapsule) included in the tablet is immediately released.

[0106] Moreover, if a film coat which can be dissolved at an objective region is executed on the surface of the tablet, the tablet itself can be dissolved at the objective region when the film coat is dissolved, so that granule containing active substance (so called microcapsule) included in the tablet is immediately released.

[0107] The tablet as set forth in claim 17 - 19 defines preferable construction of the granule containing active sub-

stance of the tablet as set forth in claim 16.

[0108] According to the tablet as set forth in claim 17, the tablet as set forth in claim 16 is characterized in that the granule containing active substance is granule containing active substance and diluting agent.

[0109] According to such a tablet, as granule containing active substance and diluting agent is used as granule containing active substance (so called microcapsule), the particle diameter and size of the granule can be easily modified by diluting agent.

[0110] Therefore, a tablet production can be easily executed by controlling the particle diameter and size of the granule so as to be easily coated with a film on the surface of the tablet.

[0111] Further, the diameter and the size of granule containing active substance can be made so as to derive the function of granule to the full extent.

[0112] According to the tablet as set forth in claim 18, the tablet in claim 16 is characterized in that the granule containing active substance is granule including active substance in base matrix.

[0113] According to such a tablet, as diluting agent used as bulking agent doesn't include lubricant, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

[0114] Further, as the tablet includes granule containing active substance in the base matrix, the base matrix can achieve its desired objective function.

[0115] For example, if the base matrix aims at prolongation of mode of action, the tablet also becomes to have a function of sustained release by the base matrix.

[0116] Therefore, if unfilmed granule containing active substance and granule containing active substance in base matrix are mixed in a tablet, they are immediately released from the tablet when the tablet is dissolved. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset of action.

[0117] As for the granule containing active substance in the base matrix, for example, if the base matrix aims at prolongation of mode of action, the tablet also becomes to have a function of prolongation of mode of action by the base matrix.

[0118] Namely, the tablet yields both rapid onset of action and prolongation of mode of action.

[0119] If the active substance is analgesic, anti-inflammatory agent, or antidote, unfilmed granule containing such agent and granule containing such agent in the base matrix are mixed. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long when a patient takes this medicine can be obtained.

[0120] The tablet as set forth in claim 19 is characterized in that the granule containing active substance of the tablet of any one of claims 16 - 18 is granule of which part containing active substance is covered with film.

[0121] According to such a tablet, as diluting agent used as bulking agent doesn't include lubricant, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

[0122] Further, as the tablet includes granule containing active substance, a film coated on the surface of the granule containing active substance brings out a desired objective function.

[0123] For example, the film coated on the granule containing active substance aims at prolongation of mode of action, the tablet also yields prolongation of mode of action because of the film.

[0124] Therefore, if unfilmed granule containing active substance and filmed granule containing active substance are mixed in a tablet, they are released from the tablet when the tablet is dissolved. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset of action.

[0125] As for the filmed granule containing active substance, for example, if the film aims at prolongation of mode of action, the tablet also becomes to have prolongation of mode of action because of the function of the film. Namely, the tablet has both rapid onset of action and prolongation of mode of action.

[0126] If the active substance is analgesic, anti-inflammatory agent, or antidote, unfilmed granule containing such agent and filmed granule containing such agent are mixed. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long when a patient takes this medicine can be obtained.

[0127] According to the tablet as set forth in claim 20, the amount of lubricant used in the tablet described in any one of claims 16 - 19 is greater than or equal to 0.0001 weight % and less than or equal to 0.2 weight percent per a tablet.

[0128] It is preferable to reduce the amount of lubricant as far as possible, preferably greater than or equal to 0.0001 weight percent and less than or equal to 0. 1 weight percent per a tablet.

[0129] Because the tablet is provided with a minute amount of lubricant on the surface, its disintegration time doesn't delay.

[0130] According to the tablet as Set forth in claim 21, the tablet described in any one of claims 15 - 20 is provided

with a dividing line on the surface thereof.

[0131] Because the tablet has a dividing line, it can be easily divided along the line. Therefore, appropriate amount of drug depending on the weight or age of a patient can be taken by a patient.

[0132] The tablet as set forth in claim 22 is characterized in that the shape of the tablet described in any one of claims 15 - 21 is anomalous.

[0133] Because the tablet has anomalous shape, drugs can be easily distinguished by its shape. Therefore, medication error is hardly happened.

[0134] The tablet as set forth in claim 23 is characterized in that the standard deviation of disintegration time of the tablet or elution time of the active substance described any one of claims 15 - 22 is less than or equal to 15 percent of average disintegrating time or average elution time.

[0135] The fact that the standard deviation of disintegration time of the tablet or elution time of the active substance can be less than or equal to 15 percent of average disintegrating time or average elution time is an effect of the experiment done by the present inventors.

[0136] Further according to the experiment done by the present inventors, it was found that the standard deviation of disintegration time of the tablet or elution time of the active substance could be less than or equal to 10.0 percent of average disintegrating time of the tablet or average elution time fo the active substance. Further it was also found that the standard deviation of disintegrating time of the tablet or elution time of the active substance could be less than or equal to 7.5 percent of average disintegrating time or average elution time, further less than or equal to 7.0 percent.

[0137] Because lubricant is uniformly applied on the surface of the tablet (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance. Therefore, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than or equal to 15.0 percent of average disintegrating time or average elution time can be easily produced.

[0138] Further, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than or equal to 10.0 percent of average disintegrating time or average elution time, which has been considered to be difficult in the prior art, can be easily produced.

[0139] Moreover, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than or equal to 7.5 percent, further 7.0 percent, of average disintegrating time or average elution time, which has been impossible to produce in the prior art as far as the inventors know, can be produced.

[0140] Because lubricant is uniformly applied on the surface of the tablet (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance.

[0141] Hence, there is no variation of the time before appearing the effect of drugs between tablets.

[0142] The tablet as set forth in claim 24 is characterized in that the lubricant of the tablet described in any one of claims 15 - 23 is magnesium stearate.

[0143] When magnesium stearate is used as lubricant, the amount of lubricant contained in the tablet can be easily measured by atomic absorption spectrometry.

Brief Description of Drawings

[0144]

Fig.1 shows a schematic construction of an enlarged view around a rotary table of a rotary type tabletting machine used for executing the present invention.

Fig.2 shows a schematic section of the enlarged view around the rotary table of the rotary type tabletting machine shown in Fig.1.

Fig.3 is a schematic view around a spraying chamber, Fig.3(a) schematically shows a construction of the spraying chamber, and Fig.3(b) schematically shows a construction of a pulsating vibration air generation means.

Fig.4 explains a concrete example of pulsating vibration air, Fig.4(a) and Fig.4(b) show negative pulsating vibration air respectively.

Fig.5 is a schematic view around a spraying chamber, Fig.5(a) schematically shows a construction of the spraying chamber, and Fig.5(b) schematically shows a construction of a pulsating vibration air generation means.

Fig.6 explains a concrete example of pulsating vibration air, Fig.6(a) and Fig.6(b) show positive pulsating vibration air respectively.

Fig.7 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.8 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.9 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.10 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.11 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.12 is a graph showing cross relationship between tabletting pressure and hardness of produced tablet.

Fig.13 is a graph showing cross relationship between time and dissolution rate.

Fig.14 is a graph showing cross relationship between time and dissolution rate.

Fig.15 schematically shows a sectional view of means (metering feeder) for quantitatively supplying lubricant contained in a hopper into a conduit.

Fig.16 is a schematic plane view showing one embodiment of an elastic membrane used for the means (metering feeder) in Fig.15.

Fig.17 schematically shows operations of the means (metering feeder) shown in Fig.15.

Fig.18 is a schematic plane view showing another embodiment of an elastic membrane used for the means (metering feeder) in Fig.15.

Fig.19 is a schematic sectional view showing another embodiment of pulsating vibration air generation means.

Fig.20 schematically explains a construction of a tablet, Fig.20(a) explains a multiple unit type tablet, Fig.20(b) and Fig.20(c) explain the construction of the granule included in the multiple unit type tablet.

Fig.21 schematically shows the tablet production method described in JP-B-41-11273.

Fig.22 schematically shows the tablet production method described in JP-A-56-14098.

Disclosure of the Invention

[0145] The present invention will be detailed hereinafter referring to the attached drawings.

(Embodiment of the Invention 1)

[0146] In this embodiment the production method of a tablet which is immediately disintegrated at an objective region will be explained referring to the attached drawings.

[0147] Here the present invention will be explained by an example using a rotary type tabletting machine.

[0148] Fig.1 shows schematic construction by enlarging one part around a rotary table of a rotary type tabletting machine used for executing the present invention.

[0149] Fig.2 is a schematic section when one part of Fig.1 around the rotary table is enlarged.

[0150] As shown in Fig.1 and Fig.2, the rotary type tabletting machine A is comprised of a rotatably provided rotary table 2 having plural dies 1, • • • in circumferential direction, plural upper punches 3, • • • and plural lower punches 4, • • • provided so as to correspond to each dies 1, • • •. A spraying chamber 8 is provided at P1 which is before a point P2 where molding material is charged in the die 1. A pulsating vibration air generation means 7 is connected to the spraying chamber 8 and a spray nozzle 9 for spraying lubricant L is provided in the spraying chamber 8. In this embodiment, an air source 10 such as a cylinder charging compressed air is connected to the spray nozzle 9 and lubricant L is designed to be sprayed from the spray nozzle 9 by the air generated from the source 10.

[0151] Next, tablet production procedure using this machine A will be explained.

[0152] The rotary table 2 is rotated at a fixed speed, pulsating vibration air is generated in the spraying chamber 8 by driving the pulsating vibration air generation means 7 when the die 1 comes to the point P1 where the spraying chamber 8 is provided according to rotation of the rotary table 2, lubricant L is simultaneously sprayed from the spray nozzle 9, and lubricant L is applied on a surface (inner wall) 1s of the die 1, a surface (lower surface) 3s of the upper punch 3, and a surface (upper surface) 4s of the lower punch 4.

[0153] Then, molding material m is charged in the die 1 which comes to the point P2 for charging molding material m in the die 1 accompanied with rotation of the rotary table 2 and extra molding material m is scraped. Thereafter, when the die 1 charged with molding material m comes to a point P3 for compressing molding material m, molding material m in the die 1 is compressed to produce a tablet by means of the upper punch 3 of which surface (lower surface) 3s is applied with lubricant L and the lower punch 4 of which surface (upper surface) 4s is applied with lubricant L. Further, when the die 1 comes to a point P4, a tablet T is discharged from the die 1 so that the tablet T is produced.

[0154] Fig.3(a) shows schematic construction around the spraying chamber 8 and Fig.3(b) illustrates construction by an example of pulsating vibration air generation means 7.

[0155] In this example, the pulsating vibration air generation means 7 is connected to the spraying chamber 8 via a conduit 13.

[0156] In Fig.3(b) the numeral 71 shows a blower, 72 shows a cylindrical tube, 73 shows a valve element provided rotatably around a rotary axis 74 so as to divide inside of the tube 72 into two parts. The conduit 13 and a conduit 14 coupled to the blower 71 are connected at a given place of the side of the tube 72. The valve element 73 is designed to

be rotated at a desired rotational velocity by means of a valve rotation control means (not shown).

[0157] When the blower 71 is rotated at a given rotation number and the valve element 73 is also rotated at a given rotational speed, the spraying chamber 8 and the blower 71 are connected as the valve element 73 is positioned at a place shown by a solid line in the figure. When the valve element 73 is positioned at a place shown by a dotted line, the spraying chamber 8 and the blower 71 are blocked off by the valve element 73. Accordingly, pulsating vibration air with its peak at atmospheric pressure and its valley at negative pressure shown in Fig. 4(a) or pulsating vibration air with its peak and valley at negative pressure shown in Fig.4(b) can be produced in the spraying chamber 8.

[0158] Here "negative pressure" means that the pressure in the spraying chamber 8 is lower than outside pressure (atmospheric pressure).

[0159] When lubricant L is sprayed from the spray nozzle 9 while generating pulsating vibration air shown in Fig.4(a) or Fig.4(b), sprayed lubricant L is diffused by the pulsating vibration air and is uniformly applied on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3 and the surface (upper surface) 4s of the lower punch 4 both of which are provided so as to correspond to the die 1 housed in the spraying chamber 8.

[0160] According to this tablet production method, as lubricant L can be uniformly applied on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3, and the surface (upper surface) 4s of the lower punch 4, molding material m can be prevented from adhering on the die 1, the upper punch 3, and the lower punch 4 of the tabletting machine A even if the amount of lubricant L sprayed in the spraying chamber 8 is only a little regardless of the kinds of active substance, diluting agent, and lubricant.

[0161] This method is characterized in that the amount of lubricant sprayed in the spraying chamber is remarkably reduced utilizing this effect. The spray amount of lubricant L to be sprayed in the spraying chamber 8 is controlled to be greater than or equal to 0.0001 weight % and less than or equal to 0.2 weight % per the weight of tablet. Further it may be controlled greater than or equal to 0.0001 weight % and less than or equal to 0.1 weight %.

[0162] According to this method, only a part of lubricant L applied on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3, and the surface (upper surface) 4s of the lower punch 4 exists on the surface of the tablet and the tablet doesn't include lubricant L therein. Therefore, the used amount of lubricant L for the tablet T is remarkably small comparing with the tablet produced by the prior production method. Hence, a problem, which has been found in the prior tablet, wherein disintegration time of tablet delays because of water repellency of lubricant L is never happened.

[0163] Further, because lubricant L isn't included in the molding material m, produced tablet can obtain practical hardness even if tabletting pressure is low (practically less than 1 ton/c m^2) comparing with the case that molding material m including lubricant L is tabletted.

[0164] Accordingly, if the tablet T produced by the production method is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and is suitable as a tablet which is required to be disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet.

[0165] If a film coat which can be dissolved at an objective region is executed on the surface of the tablet T, the tablet itself can be immediately dissolved at the objective region so that a tablet which can be dissolved at an objective region can be produced.

[0166] Further, when granule of which surface of a part containing active substance is filmed is included in a tablet as granule containing active substance, the film coated on the surface isn't destroyed at the time of compression (tabletting) because the tablet T can be compressed (tabletted) at low pressure. Accordingly, the film coated on the granule containing active substance can bring out a desired objective function.

[0167] For example, the film coated on the granule containing active substance aims at prolongation of mode of action, the tablet also has sustained release because of the film.

[0168] Therefore, if unfilmed granule containing active substance and filmed granule containing active substance are mixed in the tablet T, they are immediately released from the tablet T when the tablet T is disintegrated. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset of action.

[0169] As for the filmed granule containing active substance, for example, it the film aims at prolongation of mode of action, the tablet also becomes to have prolongation of mode of action because of the function of the film.

[0170] Namely, the tablet has both rapid onset of action and prolongation of mode of action.

[0171] If the active substance is analgesic (morphine hydrochloride and so on), anti-inflammatory agent (indometacin, diclofenac sodium and so on), or antidote(sulphyrine and so on), unfilmed granule containing such agent and filmed granule containing such agent are mixed in the tablet T. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long and also has rapid onset of action when a patient takes this medicine can be obtained.

[0172] Moreover, when granule containing active substance in a base matrix is included in the tablet T as granule containing active substance, the function of the base matrix isn't destroyed at the time of compression (tabletting)

because the tablet T can be compressed (tabletted) at low pressure. Accordingly, the base matrix can bring out a desired objective function.

[0173] Therefore, if unfilmed granule containing active substance and granule containing active substance in the base matrix are mixed in the tablet T, they are immediately released from the tablet T when the tablet T is disintegrated. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet T is disintegrated. Therefore, the tablet has superior rapid onset of action.

[0174] As for the granule containing active substance in the base matrix, for example, if the base matrix aims at prolongation of mode of action, the tablet T also becomes to have prolongation of mode of action because of the function of the base matrix.

[0175] Namely, the tablet T has both rapid onset of action and prolongation of mode of action.

[0176] If the active substance is analgesic (morphine hydrochloride and so on), anti-inflammatory agent (indometacin, diclofenac sodium and so on), or antidote(sulphyrine and so on), unfilmed granule containing such agent and granule containing such agent in the base matrix are mixed in the tablet T. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long and also has rapid onset of action when a patient takes this medicine can be obtained.

[0177] It is preferable to reduce the amount of lubricant L sprayed in the spraying chamber 8 as far as sticking of molding material m to the die 1, the upper punch 3, and the lower punch 4 of the tabletting machine A is prevented. In order to prevent that the disintegration time of the produced tablet is extended and the hardness is lowered, it is preferably greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet, although it depends on the nature of the molding material. According to an experiment, when the amount of lubricant L was greater than or equal to 0.001 weight percent and less than or equal to 0.1 weight percent per a tablet, it was found that problems such as sticking weren't caused and continuous tabletting could be executed.

[0178] Because lubricant L is uniformly applied on the surface of the tablet T (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance.

[0179] Hence, there is no variation of the time before appearing the effect of drugs between tablets.

[0180] Next, the present invention will be explained based on concrete experimental data.

(Experiment 1)

[0181] According to normal fluid-bed granulation method, polyvinyl alcohol was sprayed on the powder of which prescription was shown in the following table 1, particle was grown, and granulated material with prescribed size was manufactured. Then, the obtained granule was sized by means of a No.28 mesh. Next, it was tabletted to produce a 130mg tablet at a speed of rotating a rotary table 2 at 30 times per a minute by means of the tabletting machine A with 7mm diameter punch and die set.

[0182] When tabletting, magnesium stearate was used as lubricant. The amount of air sprayed from the nozzle 9 shown in Fig.3(a), rotation number and suction amount of the pulsating vibration air generation means 7 were controlled in such a manner that the amount of the magnesium stearate sprayed in the spraying chamber 8 was adjusted such that weight % of lubricant L included in one produced tablet became 0.03 weight % for the entire amount of the tablet.

[0183] More concretely, pulsating vibration air of which period was more than or equal to 1Hz and less than or equal to 10Hz, its valley was about 10% - 5% lower than atmospheric pressure, and its peak was almost equal to or a litter lower than atmospheric pressure was used in this experiment.

[0184] WSG-type 15 by Glatt Co., Ltd. was used as a fluid-bed granulator and HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as a main body of a tabletting machine.

Table 1

combined ingredient	weight %
Levodopa (Japanese Pharmacopoeia)	9.0
Lactose	57.5
Cornstarch	28.5
Polyvinyl alcohol	5.0
Total	100.0

(Comparison 1)

[0185] Magnesium stearate was added as lubricant for the granule produced like the experiment 1 in a ratio of 0.03 weight % for the entire amount of a tablet. After they were well mixed by a V type mixer, they were continuously tabletted by an internal lubricant method at a speed of rotating the rotary table at 30 times per minute by means of a set of 7mm punch and die so as to produce the material into a 130mg tablet. However, tablet wasn't continuously produced because molding material adhered on the punches and the dies.

[0186] Then in order to solve this, magnesium stearate was added as lubricant for the granule used in the experiment 1 in a ratio of 0.8 weight % for the entire amount of a tablet. After they were well mixed by a V type mixer, they were continuously tabletted by an internal lubricant method at a speed of rotating the rotary table at 30 times per minute by means of a set of 7mm punch and die so as to produce the material into a 130mg tablet.

[0187] However, it was hard to continuously produce a tablet because molding material adhered on the punches and the dies.

[0188] HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as the tabletting machine A.

(Comparison 2)

[0189] The granule produced like the experiment 1 was tabletted by means of a set of 7mm punch and die so as to produce a 130mg tablet. Stearate magnesium was applied on the surfaces 3s, 4s of the punches 3, 4 and the surface 1s of the die 1 according to the method described in JP-B-41-11273 so that the weight % of lubricant became 0.03 weight % per a produced tablet. Then the material was continuously tabletted at a speed of rotating the rotary table at 30 times per minute.

[0190] HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as the tabletting machine A.

[0191] Next, disintegration test according to Japanese Pharmacopoeia was executed for three kinds of tablets produced according to the experiment 1, the comparison 1, and the comparison 2 at a given test number (N=5).

[0192] The result is shown in Table 2.

Table 2

	Tabletting Pressure (ton/cm^2)	hardness (kg)	Disintegration time (min) (n = 5)
			Average measurement (standard variation)
experiment 1	0.7	9	6.0 (±0.2)
comparison 1	0.7	6	10.2 (±0.9)
comparison 2	0.7	9	8.0 (±0.6)

[0193] According to the table 2, it was found that the experiment 1 had high hardness comparing with the comparison 1 and had short disintegration time comparing with the comparisons 1 and 2. And also its disintegration time doesn't widely vary.

[0194] Also it was found that in the experiment 1 had the same hardness as the comparison 2, however, disintegration time was short and variation of disintegration time was small.

[0195] When the rotary type tabletting machine A provided with the pulsating vibration air generation means 7 shown in Fig.1 was used, it was found that the produced tablet has practical hardness at a tabletting pressure of 0.7 ton/cm^2.

[0196] As the result, it was also found that in the experiment 1 lubricant was uniformly applied on the surface of the tablet.

[0197] The standard deviation of the disintegration time of the tablet in the experiment 1 was 0.2 and the disintegration time of each tablet was less than or equal to 7%. From the above experiment, it was found that the standard deviation of the disintegration time of the tablet or the diluting time of active substance could easily become less than or equal to 15% of the average disintegration time of the tablet or the average diluting time of active substance.

[0198] Moreover according to the above experiment, it was found that the standard deviation of the disintegration time of the tablet or the diluting time of active substance could easily become less than or equal to 10% of the average disintegration time of the tablet or the average diluting time of active substance. Furthermore, it was also found that the standard deviation of the disintegration time of the tablet or the diluting time of active substance could easily become

less than or equal to 7.0% of the average disintegration time of the tablet or the average diluting time of active substance.

[0199] Therefore, it was cleared that a tablet without having variation of disintegration time and diluting time of active substance could be easily produced.

[0200] In this embodiment, the system shown in Fig.3(b) was used as a pulsating vibration air generation means 7. However, it is only an example and any kinds of system can be used as the pulsating vibration air generation means 7. For example, the blower 71 may be connected to the end of the conduit 13, a solenoid valve may be provided in the middle of the conduit 13 for opening and closing the conduit 13, the blower 71 may be rotated at a given rotation number so as to suck air in the spraying chamber 8, and the conduit 13 may be opened or closed at a prescribed period by the solenoid valve. Otherwise the blower 71 may be connected to the end of the conduit 13, the blower 71 may be rotated fast or slowly at a given period, and air in the spraying chamber 8 may be sucked strongly and weakly.

[0201] Also in the above-mentioned embodiment, the pulsating vibration air shown in Fig.4(a) or Fig.4(b) was generated. The system shown in Fig.5 may be constructed and the pulsating vibration air shown in Fig.6(a) or Fig.6(b) may be generated in the spraying chamber 8. Namely, in the embodiment shown in Fig.5, a pulsating vibration air generation means 7A is connected to the end of the conduit 13, a hopper 15 storing lubricant L is connected in midstream of the conduit 13, and a compressed air generation means 16 such as a cylinder charging compressed air is connected to the hopper 15 as shown in Fig.5(a). The numeral 17 in Fig. 5(a) shows a blower provided if required. When the blower 17 is driven, air in the spraying chamber 8 is sucked and pulsating vibration air supplied in the spraying chamber 8 and lubricant L are induced to be discharged from the spraying chamber 8.

[0202] The system shown in Fig.5 is provided with the nozzle means for spraying lubricant mixed with positive pulsating vibration air so that the construction of the spraying chamber 8 can be simplified.

[0203] As shown in Fig.5(b), the pulsating vibration air generation means 7A is provided with the blower 71, the cylindrical tube 72 connected to the conduit 13 between the blower 71 and the hopper 15, and the valve element 73 which is rotatable around the rotary axis 74 in the tube 72 and is designed to divide the inside of the tube 72 into two parts. The conduit 13 and the conduit 14 coupled to the blower 71 are connected to the side of the tube 72. The valve element 73 is constructed so as to be rotated at a desired rotational velocity by means of a valve rotation control means (not shown).

[0204] When the blower 71 is rotated at a given rotation number to send air to the spraying chamber 8 and the valve element 73 is also rotated at a given rotational velocity, the spraying chamber 8 and the blower 71 are connected when the valve element 73 is located at the place shown as a slid line in the figure. When the valve element 73 is located at a dotted line, the spraying chamber 8 and the blower 71 are blocked off by the valve element 73. Accordingly pulsating vibration air with its peak at positive pressure and its valley at atmospheric pressure as shown in Fig.6(a) is generated in the spraying chamber 8. Otherwise, pulsating vibration air with its peak and valley at positive pressure as shown in Fig.6(b) may be generated in the spraying chamber 8. While keeping this condition, the compressed air generation means 16 may be driven to feed lubricant L contained in the hopper 15 to the conduit 13 and a fixed amount of lubricant L may be supplied in the spraying chamber 8 together with the current of pulsating vibration air.

[0205] Here positive pressure means that the pressure in the spraying chamber 8 is higher than the pressure outside of the spraying chamber 8.

[0206] Otherwise, the blower 71 may be provided at the end of the conduit 13, the solenoid valve for opening and closing the conduit 13 may be provided in the midstream of the conduit 13, the blower 71 may be rotated at a given rotation number to feed air in the spraying chamber 8, the conduit 13 may be opened and closed periodically by the solenoid valve, then pulsating vibration air may be generated in the spraying chamber 8 and the conduit 13. While keeping such a condition, the compression air generation means 16 may be driven to feed lubricant L contained in the hopper 15 to the conduit 13 and a fixed amount of lubricant L is supplied in the spraying chamber 8 together with the current of pulsating vibration air. On the other hand, the blower 71 may be connected at the end of the conduit 13, the blower 71 may be rotated fast or slowly at a given period so as to feed air strongly or weekly in the spraying chamber 8, and pulsating vibration air may be generated in the spraying chamber 8 and the conduit 13. While keeping this condition, the compression air generation means 16 may be driven so as to feed lubricant L contained in the hopper 15 to the conduit 13 and a fixed amount of lubricant L may be supplied in the spraying chamber 8 together with the current of pulsating vibration air.

[0207] When pulsating vibration air shown in Fig.6(a) or Fig.6(b) is used wherein its period is more than or equal to 1Hz and less than or equal to 10Hz, its peak is about 10% - 5% higher than atmospheric pressure, and its valley is almost equal to or a litter higher than atmospheric pressure, the effect same as the experiment 1 can be obtained (same as following embodiment 2 and 3).

(Embodiment of the Invention 2)

[0208] Here, an example of producing several shapes of tablets by means of punches and a die for constructing a

female mold of a tablet with an engraved mark or a dividing line, or an anomalous tablet as the die 1, the upper punch 3, and the lower punch 4 of the rotary type tabletting machine A.

(Experiment 2)

[0209] Several anomalous tablets hawing the shape shown in Fig.7 - 11 were produced using a female mold for constructing a tablet shown in Fig. 7 - Fig.11 as the die 1, the upper punch 3, and the lower punch 4 of the rotary type tabletting machine A.

[0210] More concretely explained, according to normal fluid-bed granulation method, glybuzole and mannitol were mixed at a ratio of 7 : 3, polyvinyl alcohol was sprayed, granule having a prescribed particle size and prescribed particle size distribution was manufactured, and the obtained granule was sized by means of a No.28 mesh.

[0211] The punches 3, 4 and the die 1 for constructing a female mold of the tablets shown in Fig.7 - Fig.11 were housed in the spraying chamber 8, pulsating vibration air shown in Fig.4(a) was generated, magnesium stearate was applied as lubricant L on the surface 3s, 4s of the punches 3, 4 and the surface 1s of the die 1, and granule was continuously tabletted at a speed of rotating the rotary table 1 at 30 times per a minute by means of the lubricated punches 3, 4 and the die 1.

[0212] When tabletting, magnesium stearate was used as lubricant. The amount of air sprayed from the nozzle 9 shown in Fig.3(a), rotation number and suction amount of the pulsating vibration air generation means 7 were controlled in such a manner that the amount of the magnesium stearate sprayed in the spraying chamber 8 was adjusted such that weight % of lubricant L included in one produced tablet became 0.03 weight % for the entire amount of the tablet.

[0213] More concretely, pulsating vibration air of which period was more than or equal to 1Hz and less than or equal to 10Hz, its valley was about 10% - 5% lower than atmospheric pressure, and its peak was almost equal to or a litter higher than atmospheric pressure was used in this experiment.

[0214] WSG-type 15 by Glatt Co., Ltd. was used as a fluid-bed granulator and HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as a main body of a tabletting machine.

[0215] The tablet in Fig.7(a) shows a circular tablet generally called flat plain, the tablet in Fig.7(b) shows a circular tablet generally called shallow concave plain, the tablet in Fig.7(c) shows a circular tablet generally called normal concave plain, the tablet in Fig.7(d) shows a circular tablet generally called deep concave plain, tablet in Fig.7(e) shows a circular tablet generally called ball or pill, tablet in Fig.7(f) shows a circular tablet generally called flat beveled edge.

[0216] The tablet in Fig.8(a) shows a circular tablet generally called double radius, the tablet in Fig.8(b) shows a circular tablet generally called bevel and concave, the tablet in Fig.8(c) shows a circular tablet generally called dimple, the tablet in Fig.8(d) shows a circular tablet called ring, the tablet in Fig.8(e) shows a a circular tablet generally called rim, and the tablet in Fig.8(f) shows a capsule type tablet generally called capsule.

[0217] The tablet in Fig.9(a) shows an oval tablet generally called oval, the tablet in Fig.9(b) shows an elliptical tablet generally called ellipse, the tablet in Fig.9(c) shows a rectangular tablet generally called square, the tablet in Fig.9(d) shows a triangular tablet generally called triangle, the tablet in Fig.9(e) shows a pentangular tablet generally called pentagon, and the tablet in Fig.9(f) shows a hexagonal tablet generally called hexagon.

[0218] The tablet in Fig.10(a) shows a heptagonal tablet generally called heptagon, the tablet in Fig.10(b) shows an octagonal tablet generally called octagon, the tablet in Fig.10(c) shows a diamond-shaped tablet generally called diamond, the tablet in Fig.10(d) shows a pillow-shaped tablet generally called pillow or ballel, the tablet in Fig.10(e) shows a rectangular tablet generally called rectangle, and the tablet in Fig.10f) shows an almond-shaped tablet generally called almond.

[0219] The tablet in Fig.11(a) shows a sagittal tablet generally called arrow head, the tablet in Fig.11(b) shows a bullet-shaped tablet generally called bullet, the tablet in Fig.11(c) shows a semilunar tablet generally called half moon, the tablet shown in Fig.11(d) shows a shell-shaped tablet generally called shelled, the tablet in Fig.11(e) shows a heart-shaped tablet generally called heart, and the tablet in Fig.11(f) shows a star-shaped tablet generally called star.

(Comparison 3)

[0220] Magnesium stearate was added as lubricant for the granule produced like the experiment 2 in a ratio of 1.0 weight % for the entire amount of a tablet. After they were well mixed by a V type mixer, they were continuously tabletted by means of the punches 3, 4 and the die 1 used in the experiment 1 according to an internal lubricant method at a speed of rotating the rotary table at 30 times per minute.

[0221] WSG-type 15 by Glatt Co., Ltd. was used as a fluid-bed granulator and HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as a main body of a tabletting machine.

[0222] For each experiment 2 and comparison 3, material was continuously tabletted for 5 hours by means of punches and a die constructing a female mold shown in Fig.7 Fig.11 and produced tablet was sampled with time. Time which didn't cause sticking was measured by smoothness of produced tablet surface. In the experiment 2, sticking

wasn't happened after 5 hours. However, in the comparison 3 sticking was happened after 1 hour and inferior goods were produced.

[0223] From the above-mentioned results, it became apparent that the tablet production method of the present invention could be preferably used for producing a tablet with an engraved mark or a dividing line, or an anomalous tablet.

[0224] The same experiments as the experiment 2 and the comparison 3 were executed for a tablet with an engraved mark or a dividing line. The punches 3, 4 and the die 1 of the external lubricant spraying type tabletting machine A were housed in the spraying chamber 8, pulsating vibration air shown in Fig.4(a) was generated, magnesium stearate was applied as lubricant L on the surface 3s, 4s of the punches 3, 4 and the surface 1s of the die 1, and granule was continuously tabletted by means of the lubricated punches 3, 4 and the die 1. It was found that sticking was hardly caused for the tablet with an engraved mark or a dividing line in this case comparing with an internal lubricant method wherein material mixed with magnesium stearate as lubricant L was continuously tabletted.

(Embodiment of the Invention 3)

[0225] Here an example for producing a tablet (multiple unit tablet) including granule containing active substance (so called microcapsule) by means of the rotary type tabletting machine A shown in the embodiment of the invention 1 will be explained. (Production of Granule on which Surface is Film Coated)

1) Reference 1 (production of sustained release microcapsule granule containing theophylline as active substance)

[0226] While a mixture of 50g of theophyline, 25g of cornstarch, 25g of powder sugar was added to 900g of circular granule crystalline cellulose (brand name : CELFIA, Asahi Chemical Industry Co., Ltd.) as nuclear particle by a quantitative feeder at a rate of 10g/min mass flow rate, 100g of ethanol losution in which 5g of hydroxypropylcellulose (brand name: HPC-L, Nippon Soda Co., Ltd.) was dissolved was sprayed at a rate of 5g/min. mass flow rate , and the mixture was kneaded and granulated, using a centrifugal fluid coating means (CF-360 type, Freund Industrial Co., Ltd.). Then granule was taken out, left at rest for drying at 60°C for one hour, and uncoated granule was obtained.

[0227] 1.0kg of the obtained uncoated granule was fed in the centrifugal fluid coating means, 2000g of ethanol solution in which 100g of aminoalkylmetaacrilatecopolymer (brand name : EudragitRS, Röhm Pharma Co.,Ltd.) was dissolved was spray coated, dried through circulation at 60°C for twelve hours, then sustained release microcapsule granule was obtained (such obtained sustained release microcapsule granule is called reference 1).

2) Reference 2 (production of microcapsule formed with enteric coating)

[0228] 1.0kg of the uncoated granule obtained in the reference 1 was fed in the centrifugal fluid coating means (CF-360 type, Freund Industrial Co., Ltd.), 1500ml of water dispersions comprising 180g of aminoalkylmetaacrilatecopolymer (brand name: EudragitRS, Röhm Pharma Co., Ltd), 18g of triacetin (Yuki Gosei Kogyo Co., Ltd.), 90g of talc as a dry solid standard was sprayed on 300g of 50 mesh lactose (brand name : DMV-50M, Pharmatose Co., Ltd.) at a rate of 6ml per minute, after the film was produced 60%, dried through circulation at 60°C for twelve hours, then enteric coating microcapsule was obtained (such obtained enteric coating microcapsule granule is called reference 2).

(Experiment 3)

[0229] 700g of lactose for direct tabletting (brand name : tabletose, Taiyo Kagaku Co., Ltd.) and 300g of crystalline cellulose (brand name : AvicelPH101, Asahi Chemical Industry Co., Ltd.) were mixed with 1kg of the sustained release microcapsule granule of the reference 1 and granule for tabletting was obtained.

[0230] Magnesium stearate (Sakai Chemical Industry Co., Ltd.) was uniformly sprayed as lubricant L as dry type on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3, and the surface (lower surface) 4s of the lower punch 4 while pulsating vibration air is generated in the spraying chamber 8. The granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line. Then sustained release microcapsule tablet (multiple unit tablet) with a dividing line was obtained.

[0231] The amount of magnesium stearate contained in the obtained sustained release microcapsule tablet (multiple unit tablet) was measured. It was 0.07 weight %.

[0232] In this experiment, pulsating vibration air of which period was more than or equal to 1Hz and less than or equal to 10Hz, its valley was about 10% - 5% lower than atmospheric pressure, and its peak was almost equal to or a litter lower than atmospheric pressure was used in this experiment.

(Experiment 4)

[0233] 350g of lactose for direct tabletting and 150g of crystalline cellulose were mixed with 500g of enteric microcapsule of the reference 2 and granule for tabletting was obtained.

[0234] Magnesium stearate (Sakai Chemical Industry Co., Ltd.) was uniformly sprayed as lubricant L as dry type on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3, and the surface (lower surface) 4s of the lower punch 4 while pulsating vibration air is generated in the spraying chamber 8. The granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line as the punch 3 of the rotary type tabletting machine A shown in the embodiment of the invention 1. Then enteric microcapsule tablet (multiple unit tablet) with a dividing line was obtained.

[0235] In this experiment, pulsating vibration air of which period was more than or equal to 1Hz and less than or equal to 10Hz, its valley was about 10% - 5% lower than atmospheric pressure, and its peak was almost equal to or a litter lower than atmospheric pressure was used in this experiment.

[0236] The comparisons 4 and 5 show examples when sustained release microcapsule tablet (multiple unit tablet) with a dividing line is produced according to the prior internal lubricant method.

(Comparison 4)

[0237] 700g of lactose for direct tabletting, 280g of crystalline cellulose, and 20g of magnesium stearate as lubricant were mixed with 1kg of sustained release microcapsule granule of the reference 1 and granule for tabletting was obtained.

[0238] Then the granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line and sustained release microcapsule tablet (multiple unit tablet) with a dividing line was obtained.

(Comparison 5)

[0239] 700g of lactose for direct tabletting, 280g of crystalline cellulose, and 20g of magnesium stearate as lubricant were mixed with 1kg of enteric microcapsule granule of the reference 2 and granule for tabletting was obtained.

[0240] Then the granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line and enteric microcapsule tablet (multiple unit tablet) with a dividing line was obtained.

(Comparison 6)

[0241] In this comparison, sustained release microcapsule tablet (single unit tablet) was produced according to the prior internal lubricant method.

[0242] 25g of theophylline, 700g of lactose for direct tabletting, 265g of crystalline cellulose, and 10g of magnesium stearate as lubricant were mixed and granule for tabletting was obtained.

[0243] Then the granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line and uncoated tablet with a dividing line was obtained.

[0244] Then 2000g of ethanol dispersing liquid in which 100g of ethyl cellulose (brand name : ETHOCEL, DowChem. Co., Ltd.) was dispersed was sprayed to the obtained uncoated tablet and sustained release single unit tablet with a dividing line was obtained.

[0245] Next, relationship of tabletting pressure and hardness of tablet was examined for each experiment 3, 4, and comparison 4, 5.

(relation of tabletting pressure and hardness of tablet)

[0246] Mechanical strength (hardness) of the tablet obtained in the experiment 3, 4 and comparison 4, 5 was measured by means of tablet hardness measurement means (name : TH203CP, Toyama Sangyo Co., Ltd.).

[0247] The result is shown in table 3 and Fig.12.

Table 3

tabletting pressure (kg/punch)	Hardness			
	Experiment 3	Experiment 4	Comparison 4	Comparison 5
500	5.0	5.5	2.0	2.0
1000	10.0	11.0	4.5	5.0
1500	14.0	15.0	9.0	9.5

[0248] According to the result of the table 3 and Fig.12, a tabletting pressure over 1000kg/punch was required to obtain practical hardness (generally hardness to be destroyed at 3.7kg - 7.0kg is required) in the comparisons 4 and 5. However, it was found that adequate hardness was obtained at a tabletting pressure of 500kg/punch in the experiments 3 and 4.

[0249] From these results, it became clear that tablet with practical hardness could be produced at lower tabletting pressure than the prior art according to the present invention.

(Dissolution Test)

[0250] The tablet produced at a tabletting pressure of 500kg/punch in the experiments 3 and 4 (hereinafter called experiment 5 and experiment 6 respectively) and the tablet produced at a tabletting pressure of 1000kg/punch in the comparisons 4 and 5 (hereinafter called comparison 7 and comparison 8 respectively) were used as specimen of dissolution test.

[0251] In the dissolution test, dissolution rate was measured by a first liquid by Japanese Pharmacopoeia the 11^{th} edition for first two hours, the specimen was pulled up after two hours and transferred to a second liquid to obtain dissolution rate again according to a rotary basket method described in dissolution test of Japanese Pharmacopoeia the 11^{th} edition.

[0252] The result is shown in the following table 4 and Fig.13.

Table 4

Dissolution Time (hour)	Experiment 5	Comparison 7	Reference 1	Experiment 6	Comparison 8	Reference 2
0	0	0	0	0	0	0
0.25	5	15	5	0	30	0
0.50	12	40	10	0	70	0
0.75	15	65	15	0	95	0
1.00	22	80	20	0	100	0
1.50	30	95	30	0	100	0
2.00	41	100	40	2	100	1
2.50	51	100	50	55	100	60
3.00	61	100	60	100	100	100
4.00	82	100	80	100	100	100
5.00	100	100	100	100	100	100

[0253] From the above-mentioned results of table 4 and Fig.13, it was found that each tablet in the experiment 5 and the experiments 6 showed similar dissolution behavior as the sustained release microcapsule granule (reference 1) and the enteric microcapsule granule (reference 2) respectively. According to the above-mentioned relation of the tabletting pressure and the tablet hardness, and the result of this experiment, it became apparent6 that the film coated

on the surface of the microcapsule granule didn't cause damage while tabletting because it could be tabletted at low pressure. On the other hand, it was found that each tablet in the comparisons 7 and 8 lost sustained release function and enteric function respectively.

(Dissolution Test of Dividable Tablet)

[0254] Next, equally divided tablet of the experiments 5 and 6 and equally divided tablet of the comparison 6 were used as specimen of dissolution test and dissolution rate was obtained according to the same method of the above-mentioned dissolution test.

[0255] The result is shown in the following table 5 and Fig.14.

Table 5

Dissolution Time (hour)	Experiment 5	Experiment 5 (divided)	Experiment 6	Experiment 6 (divided)	Comparison 6	comparison 6 (divided)
0	0	0	0	0	0	0
0.25	5	7	0	0	5	40
0.50	12	13	0	0	10	75
0.75	15	16	0	0	15	90
1.00	22	23	0	0	20	100
1.50	30	41	0	1	30	100
2.00	41	52	2	3	40	100
2.50	51	64	55	60	50	100
3.00	61	83	100	100	60	100
4.00	82	100	100	100	80	100
5.00	100	100	100	100	100	100

[0256] From the above-mentioned results of table 5 and Fig.14, it was found that the tablets in the experiment 5 and the experiments 6 showed similar dissolution behavior as the sustained release microcapsule granule (reference 1) and the enteric microcapsule granule (reference 2) respectively and showed sustained release function and enteric function even if they were divided. However, the tablet in the comparison 6 lost sustained release function and enteric function when divided.

[0257] From the above results, it became apparent that the tablet (multiple unit tablet) in the present invention didn't lost sustained release function and enteric function even if they were divided.

[0258] In the embodiment of the invention 3 the multiple unit tablet of which granule surface was film coated was used. However, it is only an example. As a tablet having practical hardness can be produced at a low tabletting pressure according to the tablet production method of the present invention, a multiple unit tablet including active substance in a base matrix can be produced without destroying or plastically deforming the granule contained in the tablet.

[0259] When the amount of lubricant sprayed in the spraying chamber 8 is remarkably reduced like the embodiment of the invention 1, a tablet which doesn't contain lubricant therein and is provided with a minute amount of lubricant thereon can be produced, so that disintegration time of the tablet doesn't delay. Therefore, if the tablet is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and it is suitable as a tablet which is required to be immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet. Further, if a film which can be dissolved at an objective region is coated on the surface, the tablet can be dissolved at the objective region when the film coat is dissolved. Accordingly, it is suitably used as a tablet which is required to be dissolved at the objective region.

[0260] The inventors of the present invention measured the disintegration time of the tablet and the dissolution time of active substance produced in the experiments 1 - 4. They found that the standard deviation thereof was within 10% of the average disintegration time of the tablet and the average dissolution time of active substance.

[0261] This embodiment showed an example in which a centrifugal fluid coating machine was used to produce granule to be contained in the tablet. However, warm air which is strengthened or weakened at a prescribed period may generated in a warm air conduit at a procedure of pelletizing the granule with a desired particle size, the granule may be pelletized in such a manner that a part of powder to be granulated and material under granulated always falls to be

piled on a screen while pelletizing, and a film may be formed on the granulated material by spraying coating liquid on the granulated material. It is because that when material is granulated while warm air which is strengthened or weakened at a prescribed period may generated in the warm air conduit at a procedure of pelletizing the granule with a desired particle size, the granule may be pelletized in such a manner that a part of powder to be granulated and material under granulated always falls to be piled on a screen while pelletizing, granulated material with small specific volume can be produced comparing with the granulated material which is produced by fluidizing powder to be granulated and material under granulated by means of steady flow warm air. The granulated material becomes hard so as to be scarcely damaged at the time of tabletting, therefore, a film coated on the granulated material becomes hardly damaged.

[0262] The process for coating a film on the granulated material isn't limited to the above-mentioned fluid-bed coating method. It may be executed according to a Pan coating method or a compression coating method.

[0263] Examples of using a rotary type tabletting machine are explained in the embodiments of the invention 1 - 3, however, they are only examples and the present invention can be executed by using a single-shot tabletting machine such as an eccentric type tabletting machine other than the rotary type tabletting machine.

[0264] In the above mentioned embodiments of the invention, a system wherein a hopper 15 is connected in midstream of the conduit 13 and the compression air generation means 16 such as an air cylinder charged with compressed air is connected to the hopper 15 is explained. However, a system for discharging lubricant L stored in the hopper 15 isn't limited to such a system.

[0265] Fig.15 schematically shows a construction of such a system.

[0266] According to this system, a pulsating vibration air generation means 7A is connected to one end 13a of the conduit 13, a discharge port 15a of the hopper 15 is connected in midway of the conduit 13, and an elastic membrane 18 having an aperture (a slit in this example) 18a is provided for the discharge port 15a so as to become a bottom of the hopper 15 (see Fig.16).

[0267] The elastic membrane 18 is made of rubber such as a silicon rubber.

[0268] The member shown as 15b in Fig.15 is a lid and is provided for the hopper 15 removably and airtightly.

[0269] Next, operations of the system will be explained.

[0270] Fig.17 is an explanatory figure schematically showing operation of the system.

[0271] For using the system, the lid 15b is airtightly attached on the hopper 15 after lubricant L is contained in the hopper 15.

[0272] Then, when the pulsating vibration air generation means 7A is driven to supply positive pulsating vibration air to the conduit 13, the air pressure in the conduit 13 becomes higher than that in the hopper 15 while positive pulsating vibration air is at peak side. As shown in Fig.17(a), the elastic membrane 18 is deformed with its center curved upwardly in such a manner that the center becomes an antinode and the circumferential edge becomes a node.

[0273] In this case, the section of the aperture (slit in this example) 18a becomes V-shaped with its upper end opened. A part of lubricant L stored in the hopper 15 drops in the V-shaped aperture (slit in this example) 18a.

[0274] As positive pulsating vibration air changes from peak to valley, the air pressure in the conduit 13 is generally lowered so as to be the same as that in the hopper 15. The elastic membrane 18 is going to get back to its original shape because of its resilience as shown in Fig.17(b). The lubricant L dropped in the V-shaped aperture (slit in this example) 18a is caught in the aperture 18a.

[0275] When the positive pulsating vibration air supplied in the conduit 13 is at its valley, the air pressure in the conduit 13 becomes lower than that in the hopper 15 and the elastic membrane 18 is deformed with its center curved downwardly in such a manner that the center is antinode and the circumferential edge is node as shown in Fgl.17(c).

[0276] In this case, the section of the aperture (slit in this example) 18a becomes reverse V-shaped with its lower end opened. The lubricant L caught in the aperture 18a is discharged to the conduit 13.

[0277] Then the lubricant L discharged in the conduit 13 is immediately mixed with positive pulsating vibration air supplied in the conduit 13 to be dispersed therein and is pneumatically transported to a spraying chamber (refer to the spraying chamber 8 in Fig.5).

[0278] The elastic membrane 18 repeats up and down vibration as shown in Fig.17(a) - Fig.17(c) according to vibration amplitude, wave length, wave shape, and vibration frequency of positive pulsating vibration air.

[0279] Therefore, as long as vibration amplitude, wave length, wave shape, and vibration frequency of positive pulsating vibration air supplied in the conduit 13 are fixed, the elastic membrane 18 vibrates up and down at a fixed vibration amplitude and frequency. Accordingly the amount of lubricant L discharged in the conduit 13 via the aperture (slit in this sample) 18a is constant.

[0280] Further according to this system, because positive pulsating vibration air is supplied in the conduit 13, there are no phenomenon such as adhesion of powdered material on the inner wall of the conduit 13 and blowing-out of powdered material in the conduit 13 which have been seen in the case that steady air pressure is used for pneumatically transporting powdered material.

[0281] Therefore, according to this system, lubricant L is discharged from the other end 13b of the conduit 13 at the

same density as the lubricant L discharged to the conduit 13.

[0282] In other words this system can be functioned as a metering feeder.

[0283] Therefore, when the other end 13b of the conduit 13 is connected to the spraying chamber (refer to spraying chamber 8 in Fig.5), as long as the size of the aperture (slit in this example) 18a is fixed, and vibration amplitude, wave length, wave shape, and vibration frequency of positive pulsating vibration air supplied in the conduit 13 are fixed, lubricant L with constant density can be always supplied in the spraying chamber (refer to spraying chamber 8 in Fig.5).

[0284] Further, a media for pneumatically transporting lubricant L is air even if it is a positive pulsating vibration air so that the amount of lubricant L mixed with positive pulsating vibration air can be extremely minimized.

[0285] Accordingly, because a minute amount of lubricant L can be always sprayed in stable condition in the spraying chamber (refer to spraying chamber 8 in Fig.5), minute amount of lubricant L can be applied on the surfaces of the punches(the surface (lower surface) 3s of the upper punch and the surface (upper surface) 4s of the lower punch 4 as shown in Fig.2) and the surface (inner wall) 1s of the die 1.

[0286] In Fig.16, the elastic membrane has a slit 18a, however, this is only a preferable example. The aperture provided for the elastic membrane isn't limited to the slit 18a and the aperture may be small ones or the number isn't limited to one. For example, an elastic membrane with plural small apertures 18b may be used as shown in Fig.18.

[0287] When the size and the number of the aperture or conditions (vibration amplitude, wave length, wave shape, and vibration frequency) of positive pulsating vibration air supplied in the conduit 13 are varied, the density of lubricant L supplied in the spraying chamber (refer to the spraying chamber 8 in Fig.5) can be changed diversely.

[0288] In this embodiment, a rotary type pulsating vibration air generation means 7A shown in Fig.3(b) and Fig.5(b) wherein the valve element 73 is provided rotatably around the rotary axis 74 so as to divide inside of the tube 72 into two parts is explained as a pulsating vibration air generation means. However, it isn't limited to such means 7A.

[0289] Fig.19 shows a section of other embodiment of pulsating vibration air generation means.

[0290] The high pressure pulsating vibration air generation means 7B is provided with a valve chamber 94 having a valve seat 9. between an input port 91 and an output port 92 and a valve plug 96 which is opened and closed by a cam mechanism 95.

[0291] The cam mechanism 95 is provided with a rotary cam 97 rotatable by a driving means such as a motor (not shown) and a roller 98 attached at the lower end of the valve plug 96.

[0292] The valve seat 93 is formed with a hole narrowing into the output port 92 and the valve plug 96 is formed like a reverse mortar so as to conform to the shape of the valve seat 93 and designed to airtightly close the valve seat 93.

[0293] Further in this embodiment, an axis 96a of the valve plug 96 is provided in an axis hole 99h of a case 99 so as not to leak air and so as to be movably up and down.

[0294] The roller 98 is rotatably pinched by the rotary cam 97 and moves up and down according to a concavo-convex pattern on the rotary cam 97 while rotating.

[0295] More detailed, the rotary cam 97 is provided with an inner rotary cam 97a and an outside rotary cam 97b.

[0296] Concavo-convex pattern is provided for the inner rotary cam 97a and the outside rotary cam 97b respectively so as to keep distance of the roller 98 and to keep in line each other.

[0297] The roller 98 is pinched between the inner rotary cam 97a and the outside rotary cam 97b and is moved up and down while rotating according to the concavo-convex pattern provided for the inner rotary cam 97a and the outside rotary cam 97b by rotating the rotary cam 97 without causing jumping of the valve plug 96.

[0298] The convavo-convex pattern provided for the rotary cam 97 is selected according to physical property of lubricant L stored in the hopper 15.

[0299] In this embodiment, a flow rate control means 102 is provided for the input port 91 and compressed air which is generated by an air source 71 and of which flow rate is adjusted properly by the flow rate control means 102 is supplied in the input port 91.

[0300] Further, one end of a conduit (the conduit 13 shown in Fig.3 or Fig.5) is connected to the output port 92.

[0301] The numeral 100 in Fig.19 shows a flow rate control port provided if required. An output control valve 101 for adjusting pressure of pulsating vibration air generated from the output port 92 is provided so as to be adjustable at a desired condition from full communication to atmospheric air and shut down from atmospheric air.

[0302] Next, operational procedure for generating positive pulsating vibration air having a desired period, vibration amplitude, and wave shape by means of the high pressure pulsating vibration air generation means 7B will be explained.

[0303] The rotary cam 97 which is easy to mix lubricant L with air according to physical property of lubricant L stored in the hopper 15 is attached to a rotary axis Ma of a driving means (not shown) of the high pressure pulsating vibration air generation means 7B.

[0304] Then the air source 71 is driven and a fixed amount of compressed air is supplied to the input port 92 by adjusting the flow rate control means 102.

[0305] Further, the rotary cam 97 is rotated at a fixed rotational velocity by actuating the driving means (not shown).

[0306] The pressure of pulsating vibration air discharged from the output port 92 is controlled by adjusting the out-

put control valve 101, if required.

[0307] When the rotary cam 97 is rotated at a fixed rotational velocity, the valve plug 96 moves up and down according to the concavo-convex pattern of the rotary cam 97. Therefore, when the valve seat 93 is controlled at full closed, half opened, or full opened according to the concavo-convex pattern of the rotary cam 97, pulsating vibration air with a desired wave shape can be outputted from the output port 92.

[0308] According to the high pressure pulsating vibration air generation means 7B, rotational velocity of the rotary cam 97 may be changed by controlling the driving means (not shown) in order to obtain a desired period of pulsating vibration air discharged from the output port 92. Further, the air source 71, the flow rate control means 102, and/or the output control valve 101 may be appropriately controlled in order to obtain a desired vibration amplitude of pulsating vibration air discharged from the output port 92.

Industrial Applicability

[0309] As mentioned above, according to the tablet production method in claim 1, lubricant is sprayed at the same time pulsating vibration air is generated in the spraying chamber. When lubricant is sprayed in the spraying chamber while pulsating vibration air is generated, lubricant is mixed with pulsating vibration air.

[0310] Further according to this method, lubricant is applied on the surfaces of a pair of punches and a die while lubricant is mixed with pulsating vibration air, namely under difficult condition to apply lubricant on the surfaces thereof.

[0311] When lubricant is going to be applied on the surfaces under such a difficult condition, it can be uniformly applied on the surfaces of the pair of punches and the die.

[0312] Accordingly, as molding material is hardly adhered on the pair of punches and the die, sticking and so on aren't apt to be caused on the produced tablet in this tablet production method.

[0313] Moreover, as the result that lubricant is uniformly applied on the surfaces of the pair of punches and the die, the produced tablet hardly causes sticking and so on comparing with the prior internal lubricant method and the prior external lubricant spraying method eve if the amount of lubricant used for a tablet is remarkably reduced.

[0314] Herewith, as a tablet on which surface minute amount of lubricant is attached can be produced, the tablet produced by this method doesn't happen disintegration time delay because of water repellency of lubricant.

[0315] Therefore according to this tablet production method, a tablet which can be disintegrated at an objective region such as target region of living body can be produced.

[0316] Moreover according to the method, because molding material doesn't include lubricant therein, a tablet having practical hardness can be produced even if its tabletting pressure is lower than that of prior art when molding material is tabletted with the die and the pair of punches.

[0317] Hence, when a tablet including granule on which surface a film is coated is produced, the film formed on the surface of the granule isn't destroyed.

[0318] And when a tablet including granule containing active substance in the base matrix is produced, the function of the matrix contained in the tablet isn't damaged.

[0319] According to the tablet production method in claim 2, lubricant mixed with pulsating vibration air is designed to be sprayed in the spraying chamber.

[0320] Further according to this method, lubricant is applied on the surfaces of a pair of punches and a die while lubricant is mixed with pulsating vibration air, namely under difficult condition to apply lubricant on the surfaces thereof.

[0321] When lubricant is going to be applied on the surfaces under such a difficult condition, it can be uniformly applied on the surfaces.

[0322] Accordingly, as molding material is hardly adhered on the pair of punches and the die, sticking and so on aren't apt to be caused on the produced tablet in this tablet production method.

[0323] Moreover, as the result that lubricant is uniformly applied on the surfaces of the pair of punches and the die, the produced tablet hardly causes sticking and so on comparing with the prior internal lubricant method and the prior external lubricant spraying method eve if the amount of lubricant used for a tablet is remarkably reduced.

[0324] Herewith, as a tablet on which surface minute amount of lubricant is attached can be produced, the tablet produced by this method doesn't happen disintegration time delay because of water repellency of lubricant.

[0325] Therefore according to this tablet production method, a tablet which can be rapidly disintegrated at an objective region such as target region of living body can be produced.

[0326] Moreover according to the method, because molding material doesn't include lubricant therein, a tablet having practical hardness can be produced even if its tabletting pressure is lower than that of prior art when molding material is tabletted with the die and the pair of punches.

[0327] Hence, when a tablet including granule on which surface a film is coated is produced, the film formed on the surface of the granule isn't destroyed.

[0328] And when a tablet including granule containing active substance in a base matrix is produced, the function of the matrix contained in the tablet isn't damaged.

[0329] According to the tablet production method in claim 3, a spraying means for spraying lubricant mixed with positive pulsating vibration air is provided in the spraying chamber, so the production system can be simplified.

[0330] According to this method, a tablet with practical hardness can be produced at low tabletting pressure because lubricant isn't included in molding material. Therefore, a tablet can be produced without breaking film and granule and without causing plastic deformation even if the construction and material of the film and the base matrix aren't devised for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste.

[0331] According to the tablet production method in claim 5, a tablet with practical hardness can be produced at low tabletting pressure because lubricant isn't included in molding material. Therefore, a tablet can be produced without breaking film and granule and without causing plastic deformation even if the construction and material of the film and the base matrix aren't devised for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste.

[0332] According to the tablet production method in claim 6, a spraying means for spraying lubricant mixed with positive pulsating vibration air is required to be provided so that the system can be simplified.

[0333] According to the tablet production method in claim 7, granule containing active substance and diluting agent is used as granule containing active substance (so called microcapsule) so that the particle diameter and particle size containing active substance can be easily changed.

[0334] Therefore, a tablet can be easily produced by controlling the diameter and the size of granule containing active substance so as to facilitate coating on the surface.

[0335] Further, the diameter and the size of granule containing active substance can be made so as to derive the function of granule to the full extent.

[0336] According to the production method in claim 8, because tablet can be produced at low tabletting pressure, a tabletting can be executed without destroying the function of a base matrix even if granule contained in the tablet includes active substance in the base matrix.

[0337] According to the production method in claim 9, because tablet can be produced at low tabletting pressure, a tabletting can be executed without destroying the coating film even if granule contained in the tablet is coated with a film.

[0338] According to the tablet production method in claim 10, tabletting is continuously executed utilizing the fact that molding material isn't adhered on the punches and the dies so that sticking isn't caused. A tablet including active substance and a tablet including granule containing active substance can be produced at industrial production base.

[0339] According to the tablet production method in claim 11, tabletting is continuously executed utilizing the fact that molding material isn't adhered on the punches and the dies so that sticking isn't caused. A tablet including active substance and a tablet including granule containing active substance can be produced at industrial production base.

[0340] According to the tablet production method in claim 12, because lubricant is applied on the surface of the punches and the dies constructing a female mold for a tablet with an engraved mark or a dividing line and for an anomalous tablet in the spraying chamber in which pulsating vibration air is generated, lubricant can be applied uniformly comparing with the prior external lubricant spraying method. As a result, molding material is hardly attached on the surfaces of the punches and the dies while compressing a tablet with an engraved mark or a dividing line or an anomalous tablet so that sticking, capping, and laminating of such a tablet are prevented.

[0341] According to the tablet production method in claim 13, as tabletting pressure for compressing molding material is low, tabletting can be executed without destroying a film even if granule contained in the tablet is covered with a film. Further, if granule contained in a tablet includes active substance in a base matrix, tabletting can be executed without destroying the function of the base matrix.

[0342] According to the tablet production method in claim 14, even if the amount of lubricant sprayed at one tabletting is remarkably reduced, a tablet can be produced without causing sticking and so on. Consequently the produced tablet doesn't include lubricant therein and minute amount of lubricant is attached on the surface so that disintegration time isn't delayed.

[0343] Further according to this method, tablet can be produced at a low tabletting pressure, and the granule is hardly destroyed or plastic deformation is caused, so that the function of the granule containing active substance in the tablet isn't apt to be damaged.

[0344] Therefore, according to the production method, if the produced tablet is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and a tablet which is required to be immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet can be easily produced. Further if a film coat which can be dissolved at an objective region is executed on the surface of a tablet, the tablet itself is immediately dissolved at a desired region when a film coat is dissolved, so that a tablet which can be dissolved at an objective region can be produced.

[0345] According to the tablet in claim 15, as lubricant isn't included therein and a minute amount is attached on the surface, there is no problem such that disintegrant time of the tablet delays because of water repellency of lubricant.

[0346] Therefore, if the tablet is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and the tablet

is immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet and active substance contained in the tablet is immediately released.

[0347] Moreover, if a film coat which can be dissolved at an objective region is executed on the surface of the tablet, the tablet itself can be dissolved at an objective region when the film coat is dissolved, so that active substance contained in the tablet is immediately released.

[0348] According to the tablet in claim 16, as lubricant isn't included therein and a minute amount is attached on the surface, there is no problem such that disintegrant time of the tablet delays because of water repellency of lubricant.

[0349] Therefore, if the tablet is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and the tablet is immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet and granule containing active substance (so called microcapsule) contained in the tablet is immediately released.

[0350] Moreover, if a film coat which can be dissolved at an objective region is executed on the surface of the tablet, the tablet itself can be dissolved at an objective region when the film coat is dissolved, so that granule containing active substance (so called microcapsule) contained in the tablet is immediately released.

[0351] According to the tablet in claim 17, as granule containing active substance and diluting agent is used as granule containing active substance (so called microcapsule), the particle diameter and size of the granule can be easily modified by diluting agent.

[0352] Therefore, a tablet production can be easily executed by controlling the particle diameter and size of the granule containing active substance so as to coat a film on the surface of the tablet.

[0353] Further, the diameter and the size of granule containing active substance can be made so as to derive the function of granule to the full extent.

[0354] According to the tablet in claim 18, as diluting agent used as bulking agent doesn't include lubricant, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

[0355] Further, as the tablet includes granule containing active substance in the base matrix, the base matrix can achieve its desired objective function.

[0356] For example, if the base matrix aims at prolongation of mode of action, the tablet also becomes to have a function of sustained release by the base matrix.

[0357] Therefore, if unfilmed granule containing active substance and granule containing active substance in base matrix are mixed in a tablet, they are immediately released from the tablet when the tablet is dissolved. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset of action.

[0358] As for the granule containing active substance in the base matrix, for example, if the base matrix aims at prolongation of mode of action, the tablet also becomes to have a function of prolongation of mode of action by the base matrix.

[0359] Namely, the tablet has both rapid onset of action and prolongation of mode of action.

[0360] If the active substance is analgesic, anti-inflammatory agent, or antidote, unfilmed granule containing such agent and granule containing such agent in the base matrix are mixed. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long when a patient takes this medicine can be obtained.

[0361] According to the tablet in claim 19, as diluting agent used as bulking agent doesn't include lubricant, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

[0362] Further, as the tablet includes granule containing active substance, a film coated on the surface of the granule containing active substance brings out a desired objective function.

[0363] For example, the film coated on the granule containing active substance aims at prolongation of mode of action, the tablet also has prolongation of mode of action because of the film.

[0364] Therefore, if unfilmed granule containing active substance and filmed granule containing active substance are mixed in a tablet, they are immediately released from the tablet when the tablet is dissolved. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset of action.

[0365] As for the filmed granule containing active substance, for example, if the film aims at prolongation of mode of action, the tablet also becomes to have prolongation of mode of action because of the function of the film.

[0366] Namely, the tablet has both rapid onset of action and prolongation of mode of action.

[0367] If the active substance is analgesic, anti-inflammatory agent, or antidote, unfilmed granule containing such agent and filmed granule containing such agent are mixed. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long when a patient takes this medicine can be obtained.

[0368] Because the tablet in claim 20 is provided with a minute amount of lubricant on the surface, its disintegration time doesn't delay.

[0369] As the tablet in claim 21 has a dividing line, it can be easily divided along the line. Therefore, appropriate amount of drug depending on the weight or age of a patient can be taken by a patient.

[0370] Because the tablet in claim 22 has anomalous shape, drugs can be easily distinguished by its shape. Therefore, medication error is hardly happened.

[0371] According to the tablet in claim 23, because lubricant is uniformly applied on the surface of the tablet (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance. Therefore, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than 15.0 percent of average disintegrating time or average elution time can be easily produced.

[0372] Further, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than 10.0 percent of average disintegrating time or average elution time, which has been considered to be difficult in the prior art, can be easily produced.

[0373] Moreover, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than 7.5 percent of average disintegrating time or average elution time, which has been impossible to produce in the prior art as far as the inventors know, can be produced.

[0374] Because lubricant is uniformly applied on the surface of the tablet (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance.

[0375] Hence, there is no variation of the time before appearing the effect of drugs between tablets.

[0376] According to the tablet in claim 24, as magnesium stearate is used as lubricant, the amount of lubricant contained in the tablet can be easily measured.

Claims

1. A production method of a tablet including at least active substance by means of a die and a pair of punches, comprising steps of;

   preparing molding material including said active substance;
   housing said die and said pair of punches in a spraying chamber;
   generating pulsating vibration air and spraying lubricant mixed in air in said spraying chamber;
   applying lubricant on the surfaces of said die and said pair of punches housed in said spraying chamber while the lubricant sprayed in said spraying chamber is mixed with said pulsating vibration air; and
   tabletting said molding material by means of said die and said pair of punches on which surfaces said lubricant is applied.

2. A production method of a tablet including at least active substance by means of a die and a pair of punches, comprising steps of;

   preparing molding material including said active substance;
   housing said die and said pair of punches in a spraying chamber;
   spraying lubricant mixed in pulsating vibration air in said spraying chamber;
   applying lubricant on the surfaces of said die and said pair of punches housed in said spraying chamber; and
   tabletting said molding material by means of said die and said pair of punches on which surfaces said lubricant is applied.

3. The tablet production method as set forth in claim 2, wherein said pulsating vibration air is a positive pulsating vibration air.

4. A production method of a tablet including at least granule containing active substance by means of a die and a pair of punches, comprising steps of;

   mixing granule containing active substance and diluting agent uniformly and preparing molding material including said granule containing active substance;
   housing said die and said pair of punches in a spraying chamber;
   generating pulsating vibration air and spraying lubricant mixed in air in said spraying chamber;
   applying lubricant on the surfaces of said die and said pair of punches housed in said spraying chamber while the lubricant sprayed in said spraying chamber is mixed with said pulsating vibration air; and
   tabletting said molding material including granule containing said active substance by means of said die and said pair of punches on which surfaces said lubricant is applied.

5. A production method of a tablet including at least granule containing active substance by means of a die and a pair of punches, comprising steps of;

mixing granule containing active substance and diluting agent uniformly and preparing molding material including said granule containing active substance;
housing said die and said pair of punches in a spraying chamber;
spraying lubricant mixed in pulsating vibration air in said spraying chamber;
applying lubricant on the surfaces of said die and said pair of punches housed in said spraying chamber; and
tabletting said molding material including granule containing said active substance by means of said die and said pair of punches on which surfaces said lubricant is applied.

6. The tablet production method as set forth in claim 5, wherein said pulsating vibration air is a positive pulsating vibration air.

7. The tablet production method as set forth in any one of claims 4 - 6, wherein said granule containing active substance is granule including active substance and diluting agent.

8. The tablet production method as set forth in any one of claims 4-6, wherein said granule containing active substance is granule including active substance in base matrix.

9. The tablet production method as set forth in any one of claims 4 - 8, wherein said granule containing active substance is granule of which part containing active substance is covered with film.

10. The tablet production method as set forth in claim 1 or 4, wherein following steps are continuously executed;

preparing molding material including said active substance;
housing said die and said pair of punches in said spraying chamber;
generating pulsating vibration air, spraying lubricant mixed in air in said spraying chamber, and applying the lubricant on the surfaces of said die and said pair of punches while the lubricant sprayed in said spraying chamber is mixed with pulsating vibration air; and
tabletting said molding material by means of said die and said pair of punches on which surfaces said lubricant is applied.

11. The tablet production method as set forth in claim 2 or 5, wherein following steps are continuously executed;

preparing molding material including said active substance;
housing said die and said pair of punches in said spraying chamber;
spraying lubricant mixed in positive pulsating vibration air in said spraying chamber, and applying the lubricant on the surfaces of said die and said pair of punches; and
tabletting said molding material by means of said die and said pair of punches on which surfaces said lubricant is applied.

12. The tablet production method as set forth in any one of claims 4 - 11, wherein said punches and said die construct a female mold of a tablet having an engraved mark or a dividing line and an anomalous tablet.

13. The tablet production method as set forth in any one of claims 1 - 12, wherein tabletting pressure of said step for tabletting said molding material by means of said lubricated die and pair of punches is low.

14. The tablet production method as set forth in any one of claims 1 - 13, wherein the amount of lubricant sprayed in said spraying chamber is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

15. A tablet containing active substance, wherein lubricant is provided only on the surface thereof and amount of lubricant is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

16. A tablet including granule containing active substance in diluting agent, wherein lubricant is provided only on the surface thereof.

17. The tablet as set forth in claim 16, wherein said granule containing active substance is granule containing active substance and diluting agent.

18. The tablet as set forth in claim 16, wherein said granule containing active substance is granule including active substance in base matrix.

19. The tablet as set forth in any one of claims 16 - 18, wherein said granule containing active substance is granule of which part containing active substance is covered with film.

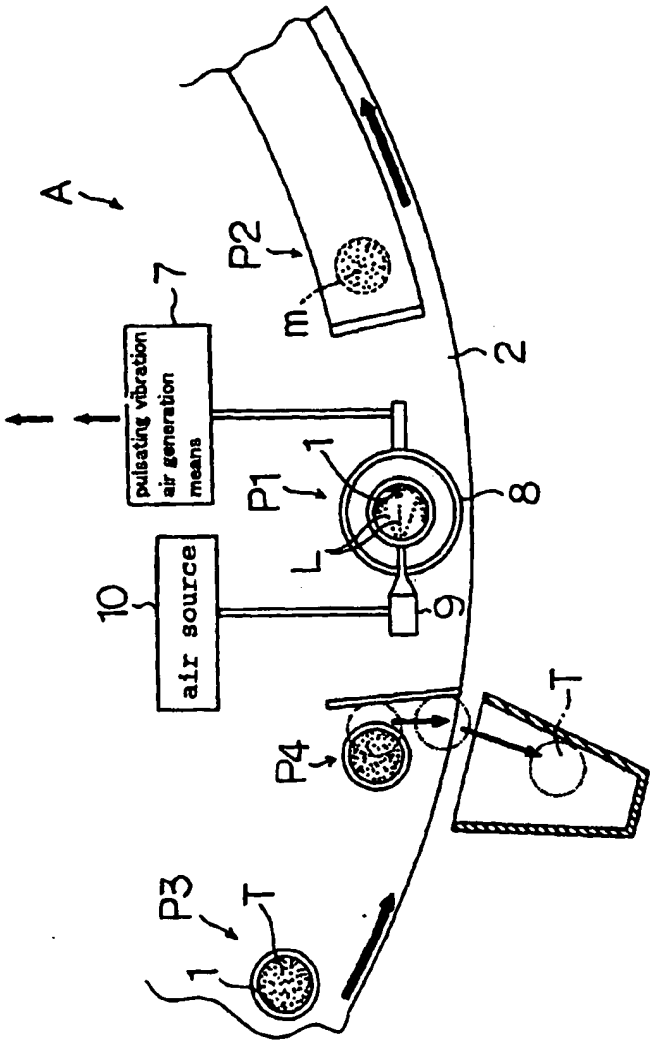
20. The tablet as set forth in any one of claims 16 - 19, wherein amount of lubricant is greater than or equal to 0.0001 weight % and less than or equal to 0.2 weight percent per a tablet.

21. The tablet as set forth in any one of claims 15 - 20, wherein a dividing line for dividing the tablet is provided on the surface thereof.

22. The tablet as set forth in any one of claims 15 - 21, wherein shape of the tablet is anomalous.

23. The tablet as set forth in any one of claims 15 - 22, wherein standard deviation of disintegrating time of the tablet or elution time of the active substance is less than or equal to 15 percent of average disintegrating time or average elution time.

24. The tablet as set forth in any one of claims 15 - 23, wherein said lubricant is magnesium stearate.


A
P2
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pulsating vibration air generation means
P1
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air source
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P3
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Fig.1

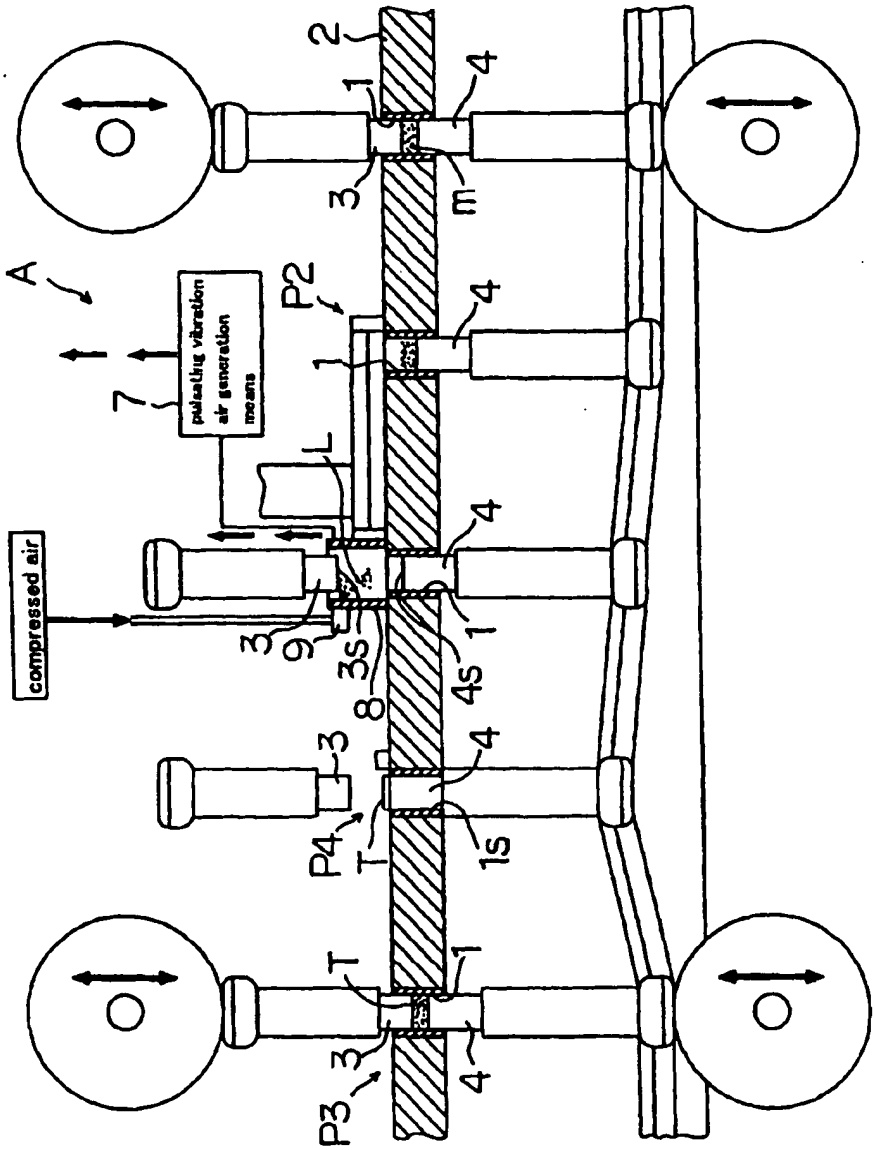
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Fig.2

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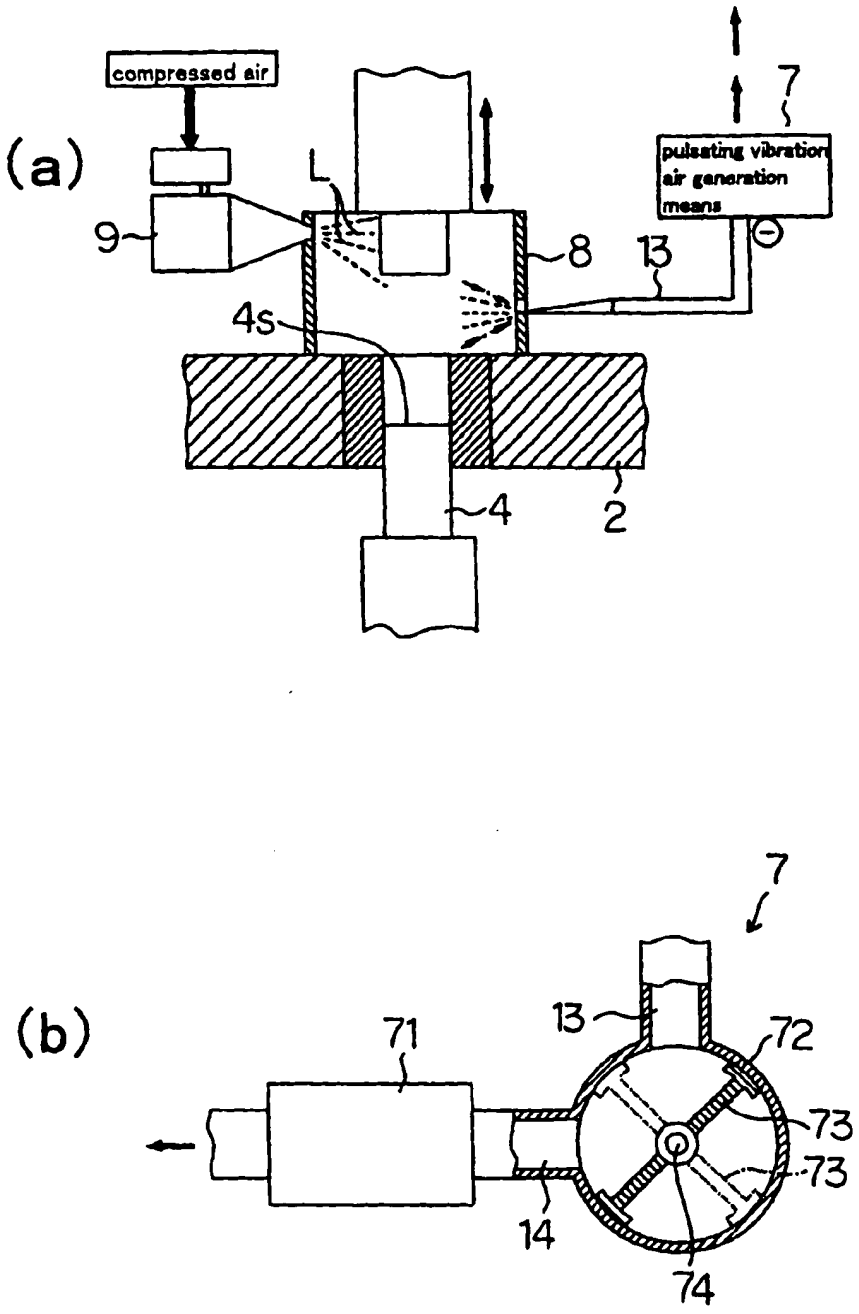
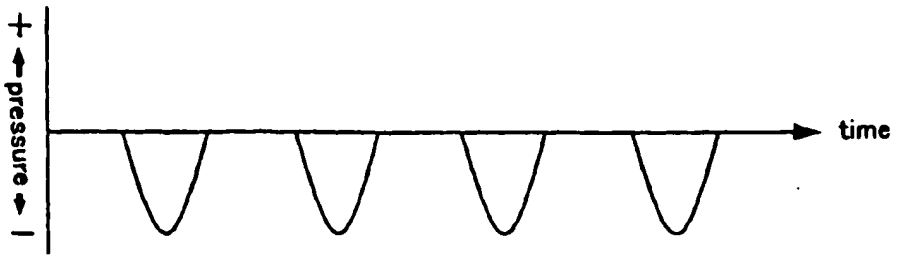

(a)
compressed air
9
L
8
13
7
pulsating vibration air generation means
4s
4
2
(b)
7
13
71
72
73
73
14
74

Fig.3

(a)



(b)

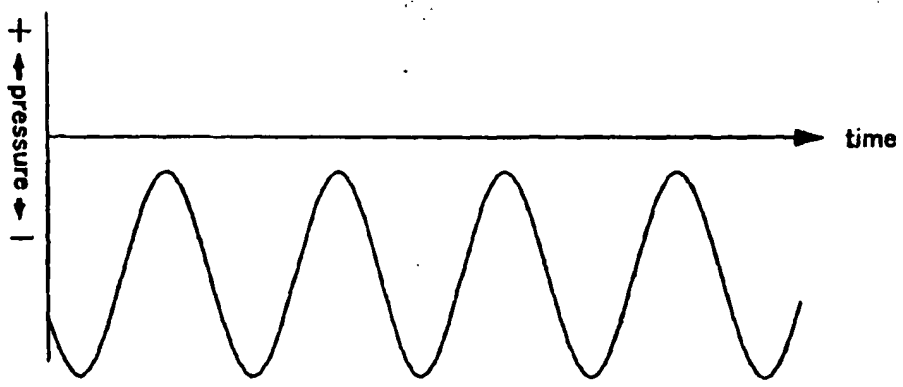


Fig.4

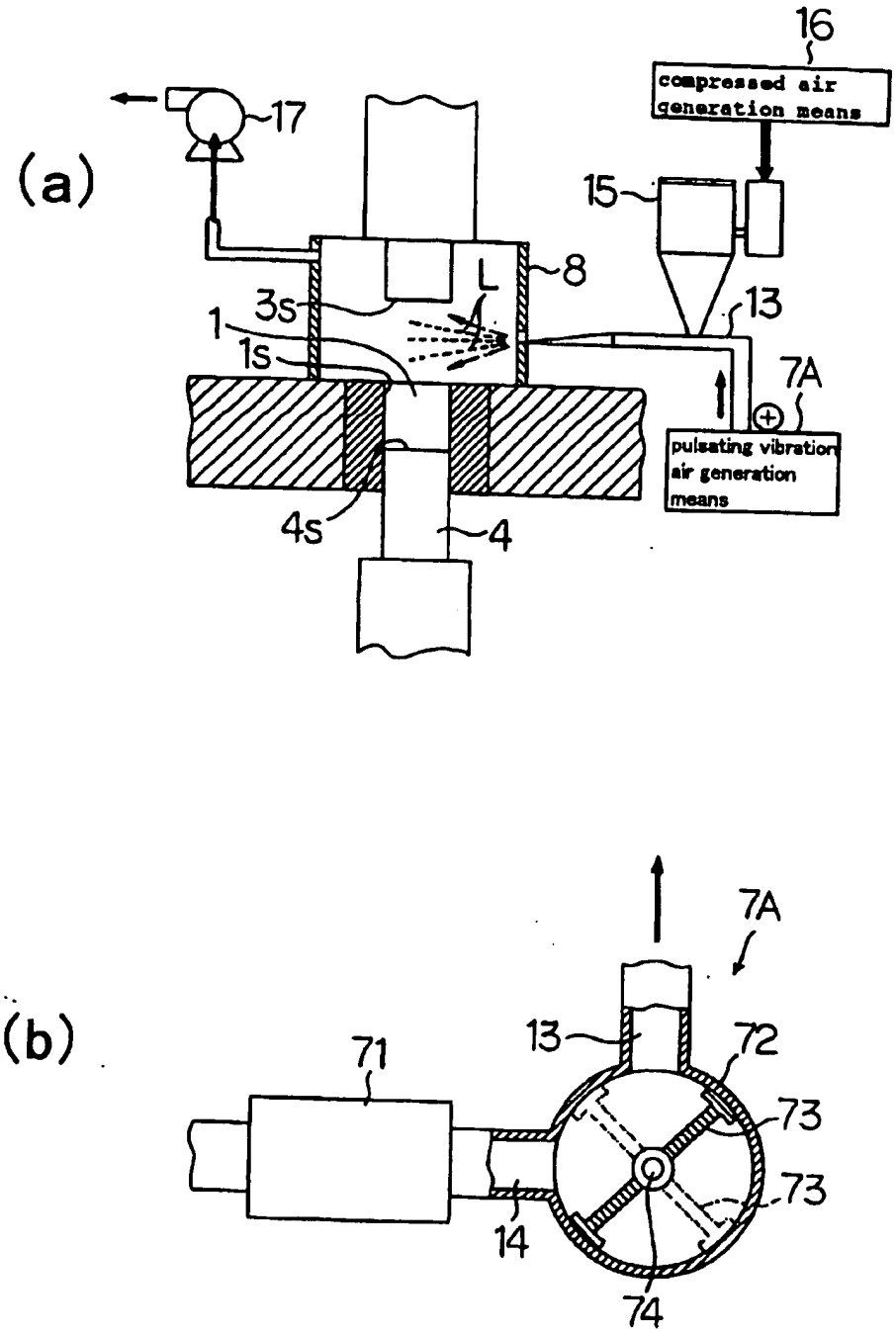

(a)
16
compressed air generation means
17
15
8
L
3s
1
1s
13
7A
pulsating vibration air generation means
4s
4
(b)
7A
13
72
71
73
73
14
74

Fig.5

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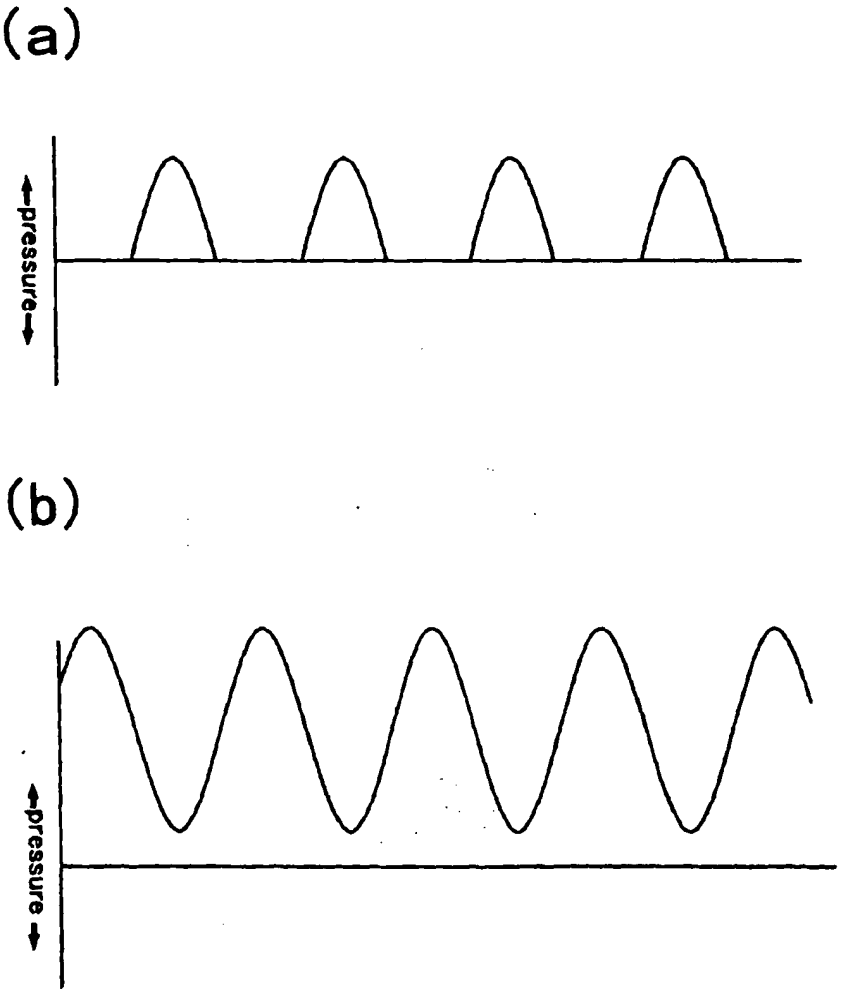


Fig.6

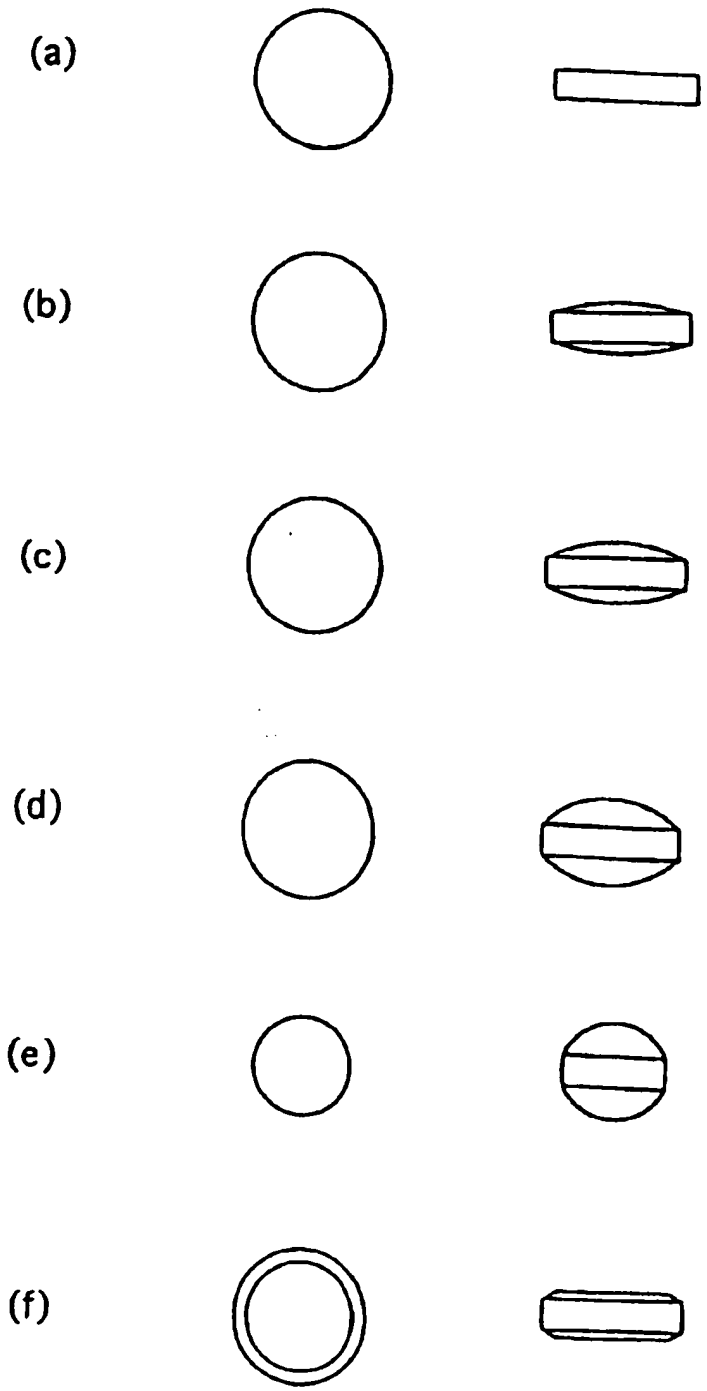


Fig.7

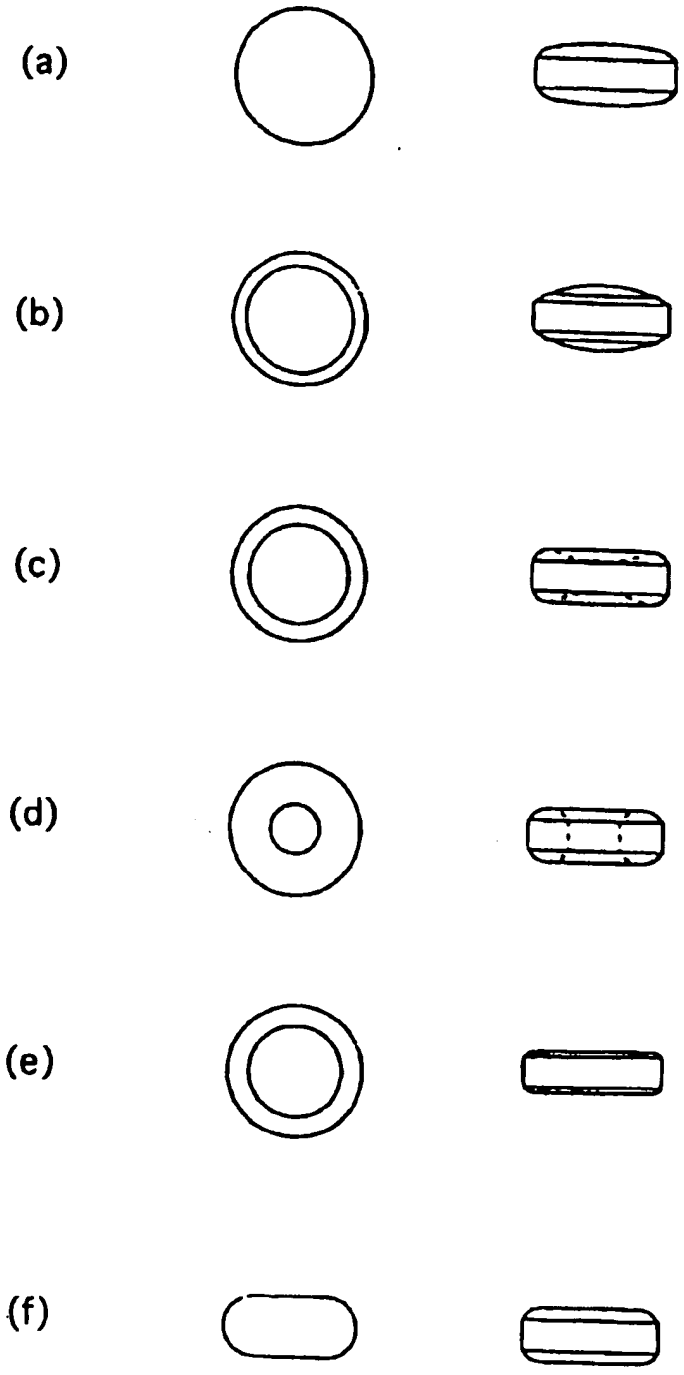


Fig.8

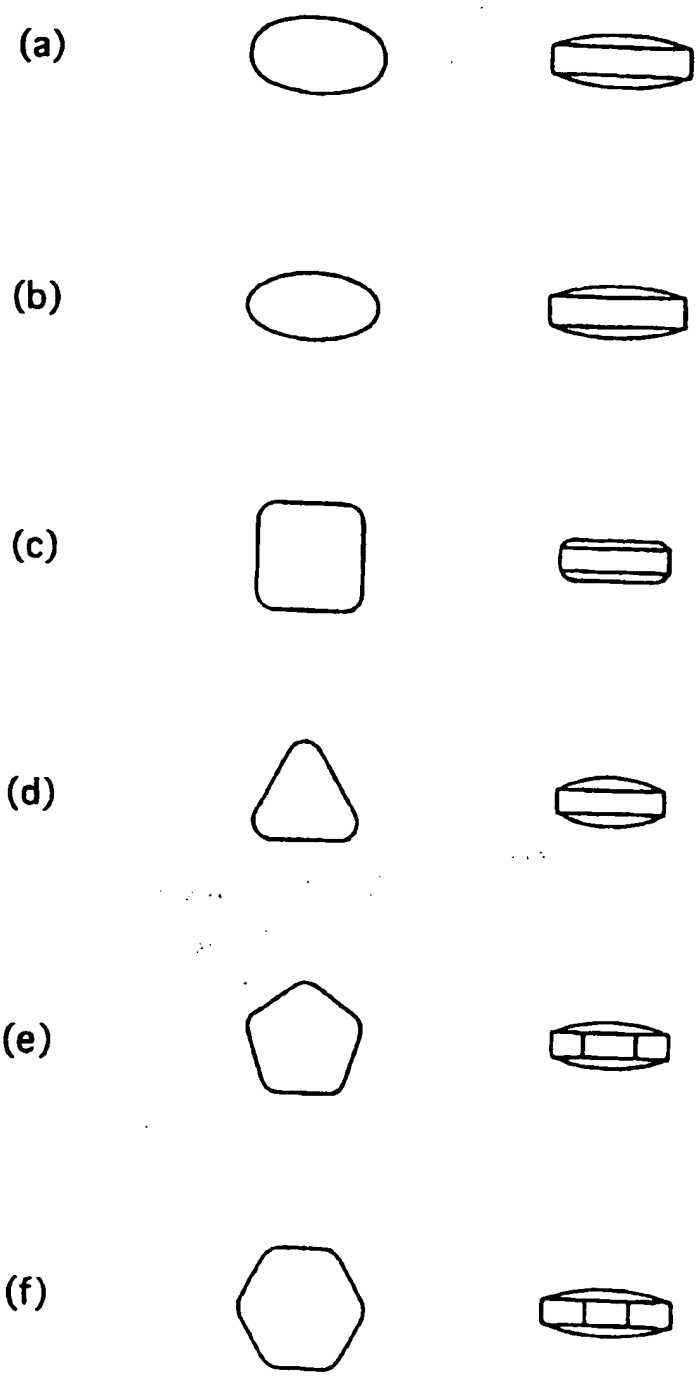


Fig.9

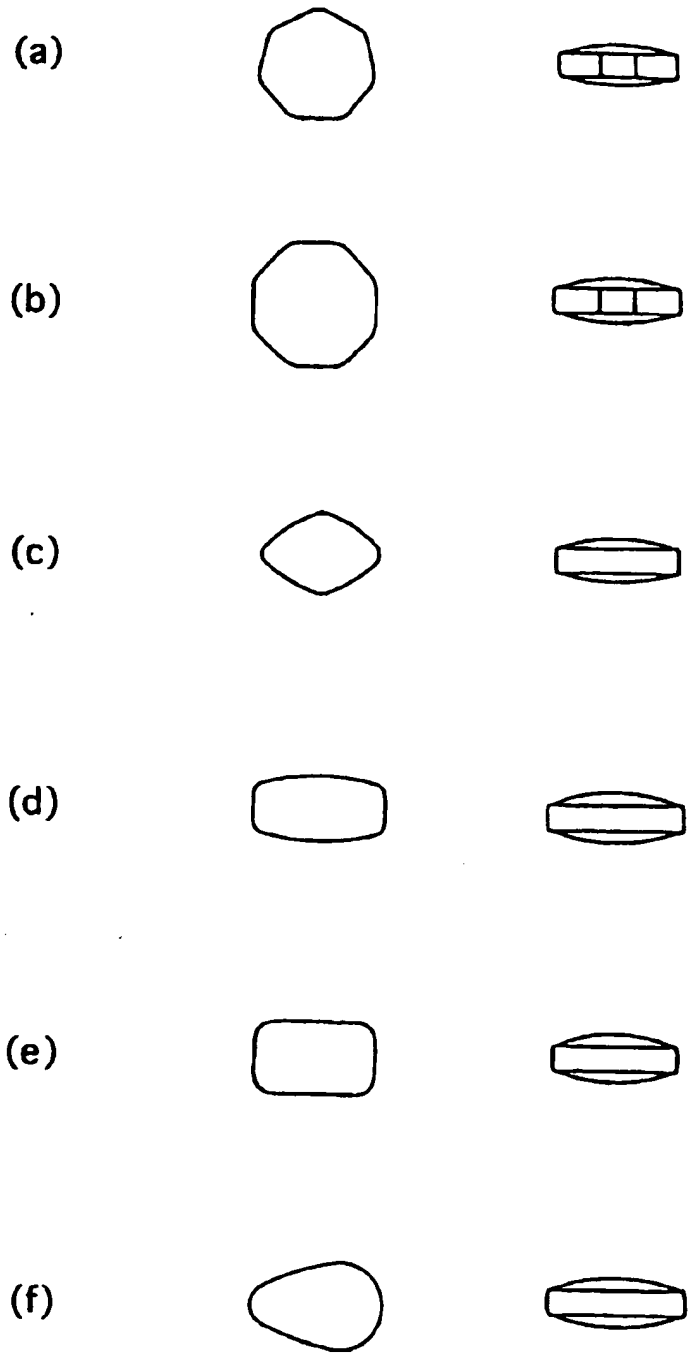


Fig.10

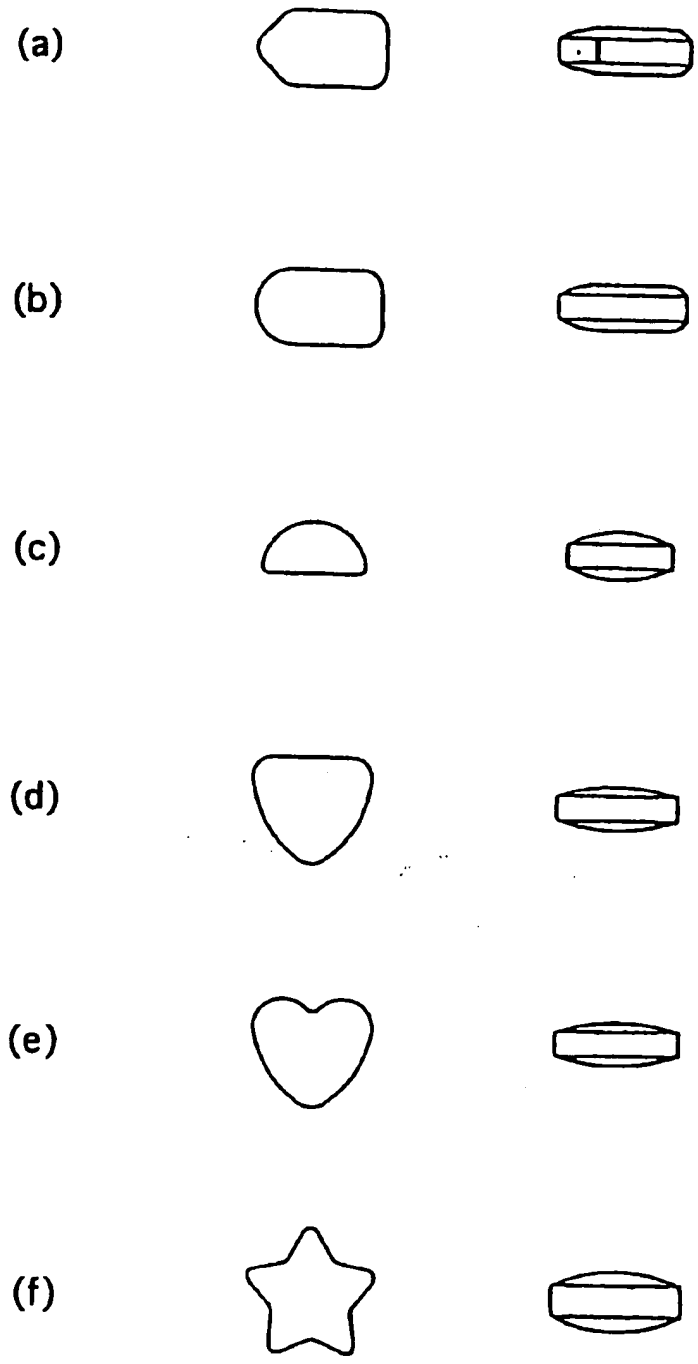


Fig.11

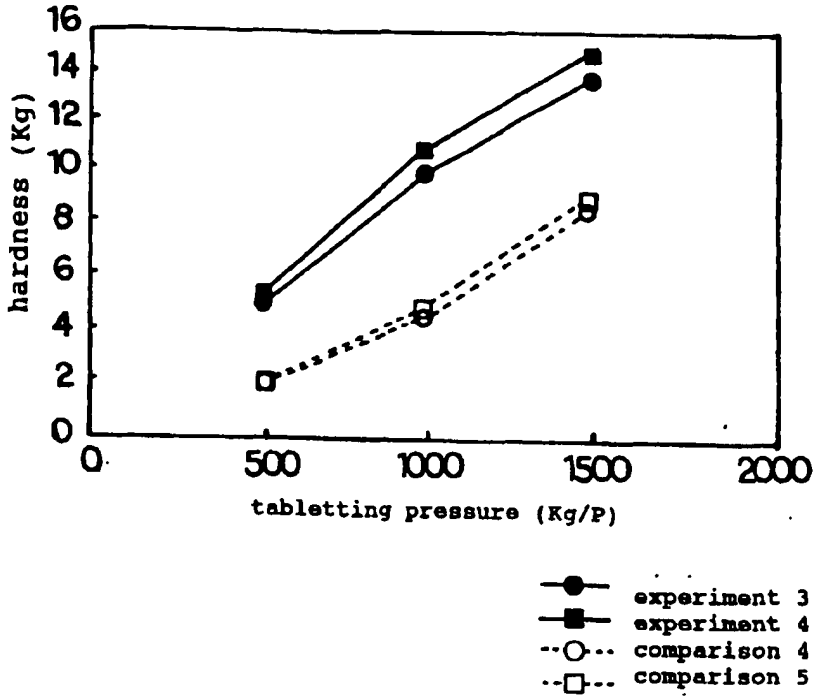
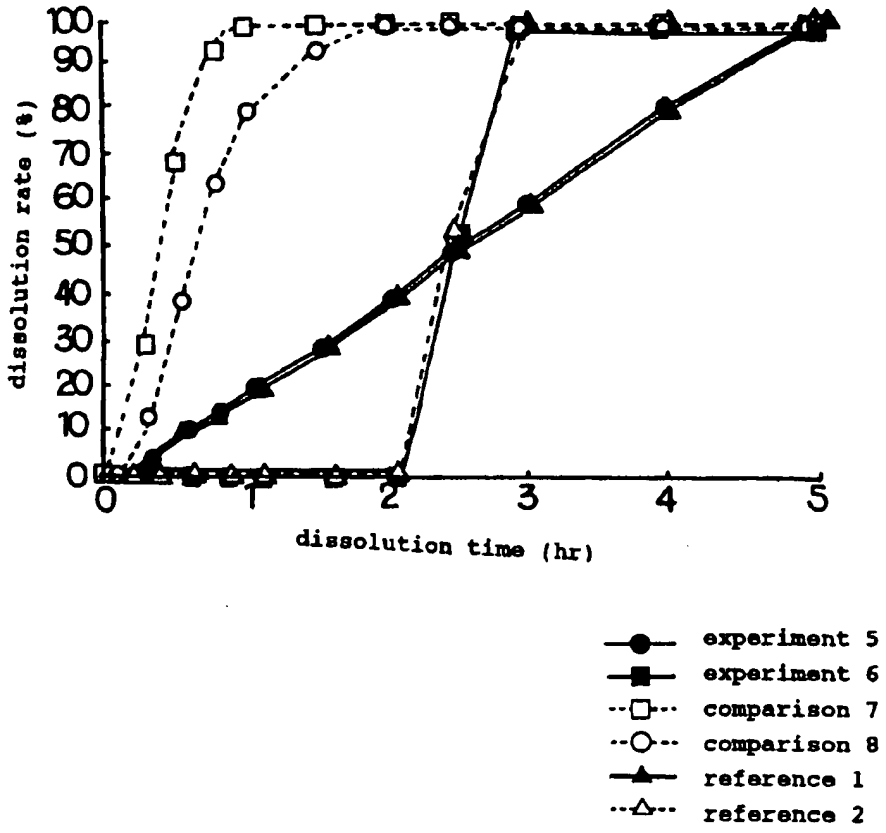


Fig.12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100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
dissolution time (hr)
experiment 5
experiment 6
comparison 7
comparison 8
reference 1
reference 2

Fig.13

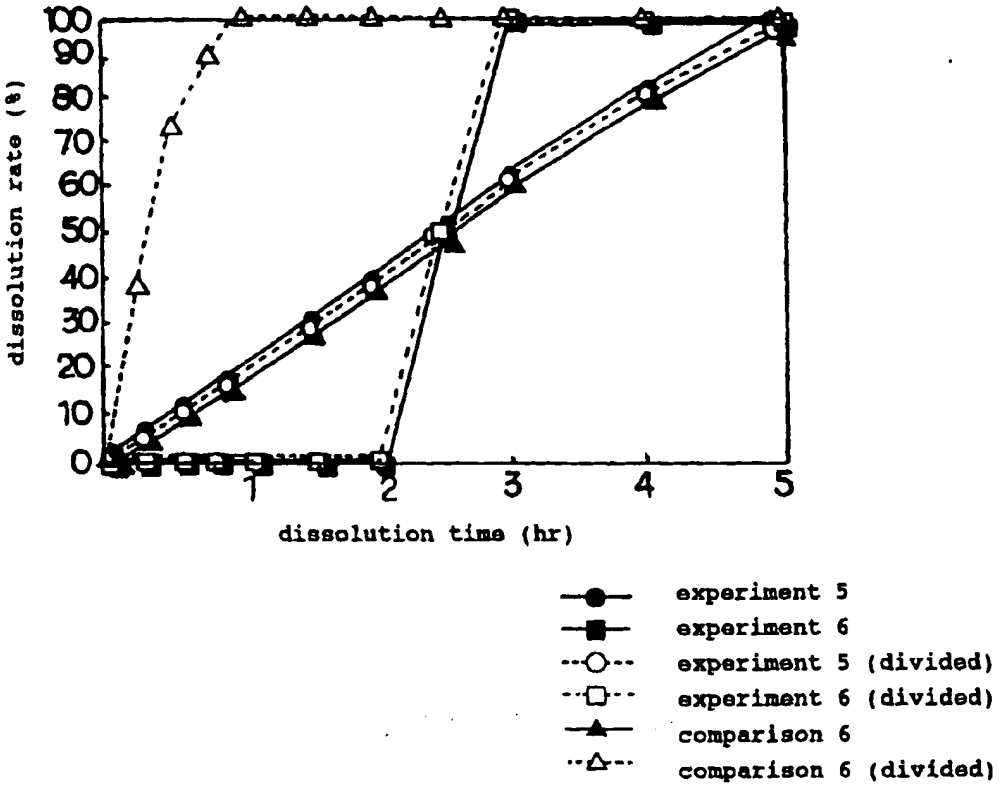

dissolution rate (%)
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
dissolution time (hr)
experiment 5
experiment 6
experiment 5 (divided)
experiment 6 (divided)
comparison 6
comparison 6 (divided)

Fig.14

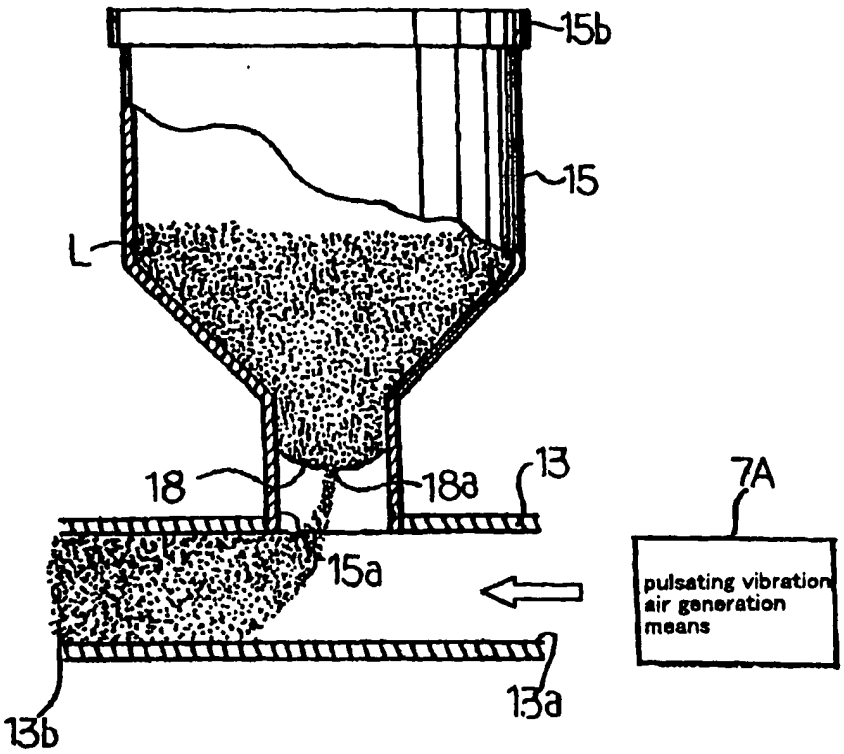


Fig.15

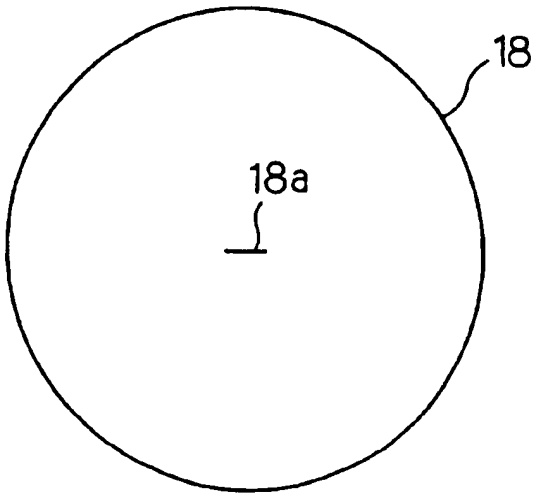


Fig.16

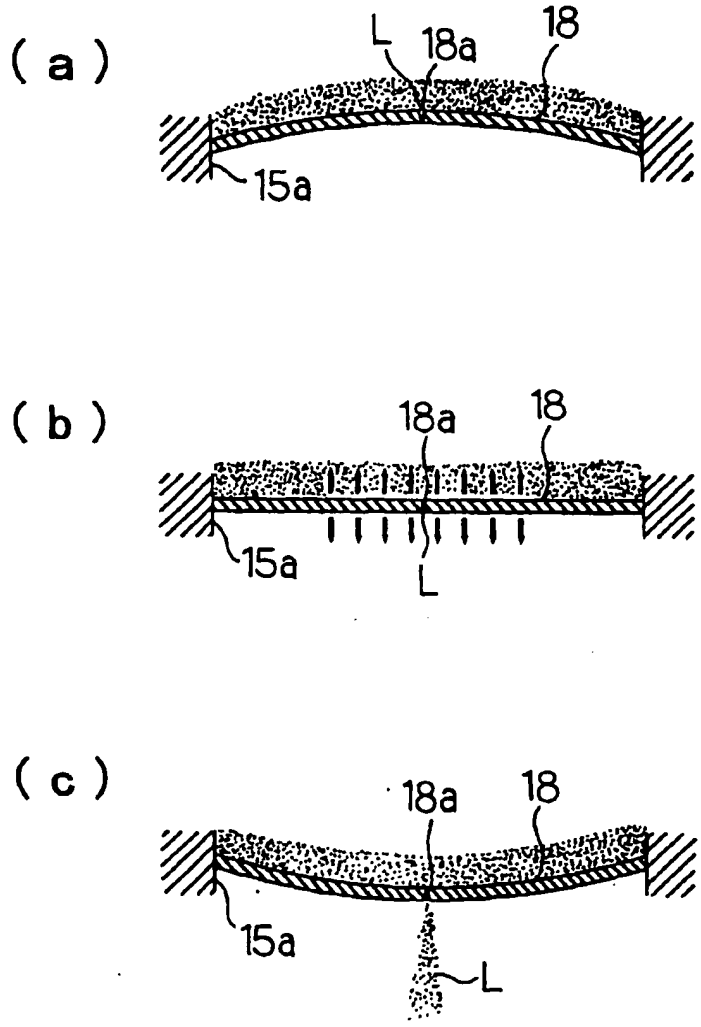


Fig.17

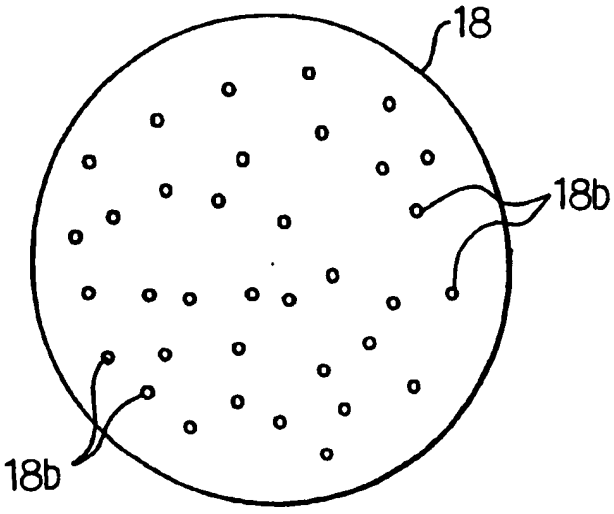


Fig.18

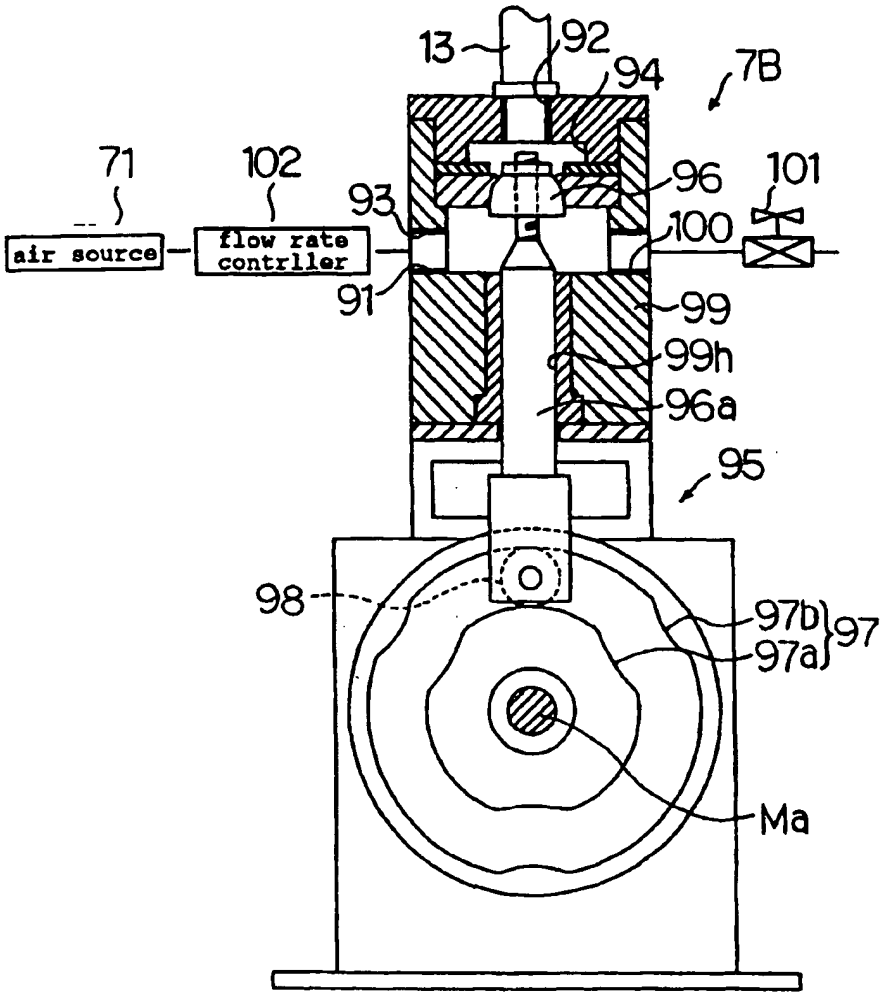


Fig.19

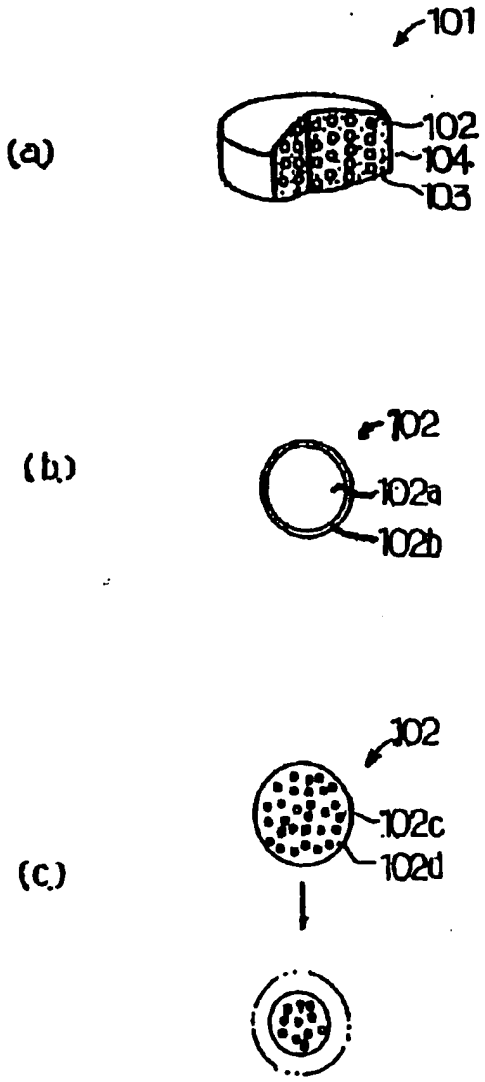


Fig.20

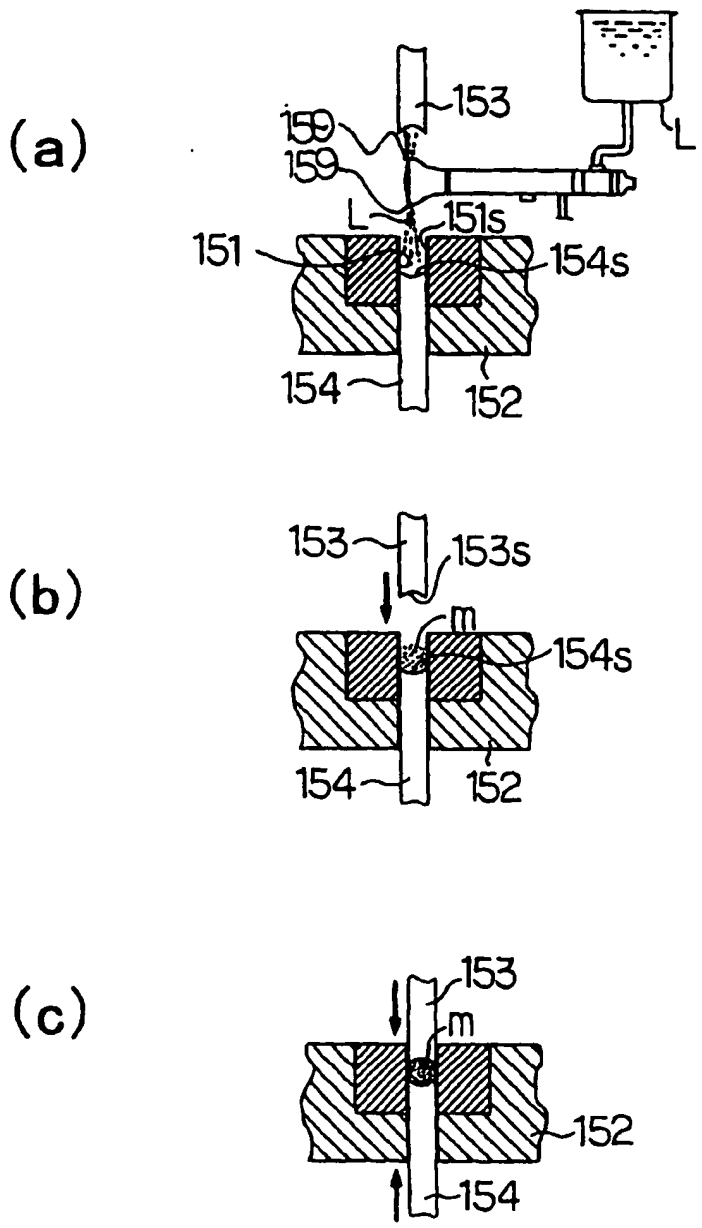
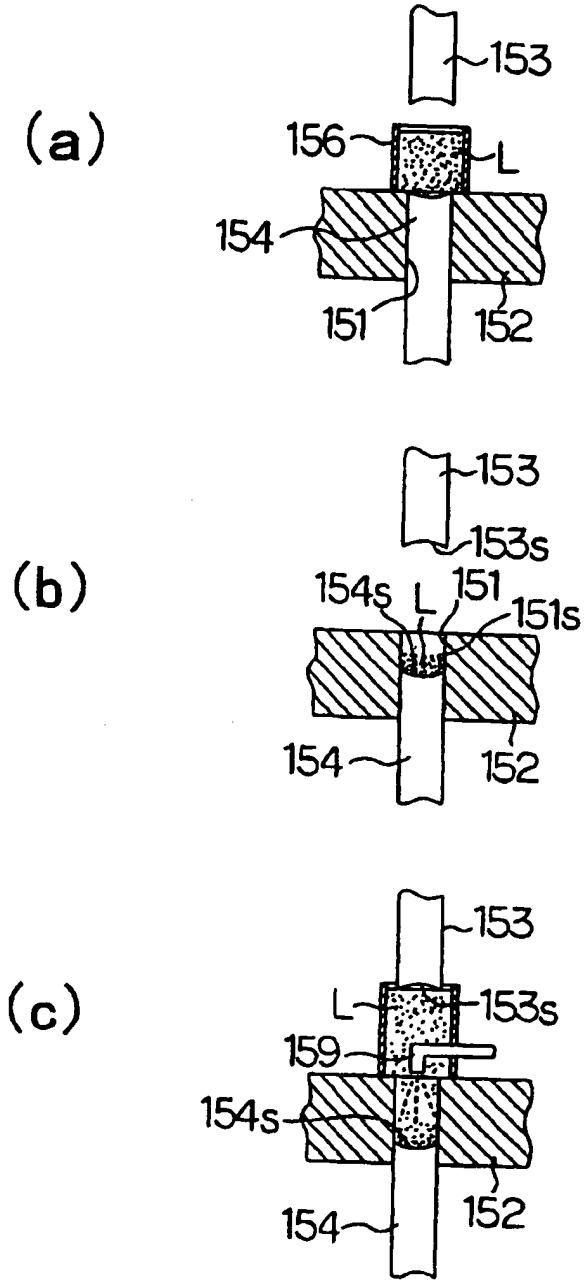


Fig.21


(a)
153
156
L
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151
152
(b)
153
153s
154s
L
151
151s
154
152
(c)
153
L
153s
159
154s
154
152

Fig.22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/01939

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] A61J3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] A61J3/10, B30B11/00, 11/08, A61K9/00-9/72, 47/00-47/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Toroku Jitsuyo Shinan Koho 1994-1999
Kokai Jitsuyo Shinan Koho 1971-1999 Jitsuyo Shinan Toroku Koho 1996-1999

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	JP, 7-124231, A (Kyowa Hakko Kogyo Co., Ltd.), 16 May, 1995 (16. 05. 95), Full text ; all drawings & EP, 650826, A1 & US, 5700492, A	1-8, 10, 11 14-18, 20, 24 9, 12, 13 21-23
X Y	JP, 6-190267, A (Fuso Pharmaceutical Industries, Ltd.), 12 July, 1994 (12. 07. 94), Par. Nos. [0020], [0022] (Family: none)	15-20, 23, 24 9, 12-14 21, 22
X Y	JP, 62-187598, A (University of Bath), 15 August, 1987 (15. 08. 87), Full text ; all drawings & GB, 2183538, A & EP, 225803, A & US, 4832880, A	15-18, 20, 24 14
Y	JP, 8-277218, A (Kyowa Hakko Kogyo Co., Ltd.), 22 October, 1996 (22. 10. 96), Claims 1, 3 ; Figs. 1, 2 (Family: none)	12-14, 21-24

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 July, 1999 (08. 07. 99)	21 July, 1999 (21. 07. 99)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)